Effect of Cognitive, Impairment-Oriented and Task-Specific Interventions onBalance and Locomotion Control

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Contributions of authors

Chapter 1 provides an introduction of the main topics that were included in the different research studies presented in this thesis. Additionally, introduce the research questions and aims proposed in this thesis. **Chapter 2** provides a review of the literature that places my dissertation in the context of the larger field and highlights the significance of the research questions included in my thesis. Dr. Tanvi Bhatt and Ms. Julia Lerman assisted with editing this chapter. **Chapter 3** correspond to a published study *(Varas-Diaz, G., Kannan, L., & Bhatt, T. (2020). Effect of Mental Fatigue on Postural Sway in Healthy Older Adults and Stroke Populations. Brain sciences, 10(6), 388.)* for which I was the primary author. Lakshmi Kannan provided significant contribution in data collection and analysis, and Dr. Tanvi Bhatt contributed significantly in the experimental design, and editing the manuscript as well as founding the research project. **Chapter 4** is another manuscript which is under review in Journal of Aging and Physical Activity (*Gonzalo Varas-Diaz, Udai Jayakumar, Bradforf Taras, Shuaijie Wang, Tanvi Bhatt. Assessing balance loss and stability control in older adults exposed to gait perturbations: A feasibility study of a moving platform simulating slips and trips*.) for which I was the primary author. I primarily worked on the data collection and analysis along with the writing and editing of the manuscript with the help of Dr. Tanvi Bhatt and Dr. Jayakumar. Dr. Shuaijie Wang contributed significantly in data analysis and processing, Bradfort Taras contributed with the experimental setup and editing the manuscript. Dr. Tanvi Bhatt and Dr. Udai Jayakumar contributed significantly in the experimental design and editing the manuscript as well as founding the research project. **Chapter 5** is another manuscript which is ready for submission and in which I am the first author. I primarily worked on the data collection and analysis along with the writing and editing of the manuscript with the help of Dr. Tanvi Bhatt. Dr. Tanvi Bhatt contributed significantly in the experimental design and editing the manuscript as well as founding the research project. **Chapter 6** correspond to an accepted for publication manuscript in Physiotherapy Theory and Practice Journal, and in which I am the primary author *(Gonzalo Varas-Diaz,Paul Cordo, Shamali Dusane, Tanvi Bhatt. (2021). Effect of robotic-assisted ankle training on gait in stroke participants: A case report)*. I primarily worked on the data collection and analysis along with the writing and editing of the manuscript with the help of Dr. Tanvi Bhatt. Dr. Shamali Dusane contributed with data collection and analysis. Dr.

Paul Cordo and Dr. Tanvi Bhatt contributed significantly with data analysis, experimental design, data analysis and editing the manuscript as well as founding the research project. **Chapter 7** represents the synthesis of my results, conclusions, and future directions of the research presented in this dissertation. Dr. Tanvi Bhatt assisted with editing this chapter.

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List of abbreviations

PwS: Persons with stroke.

PwCS: Persons with chronic stroke.

NMES: neuromuscular electrical stimulation.

ROM: range of motions.

CNS: central nervous system.

SOT: Sensory Organization Test.

IOT: Impairment-oriented therapy.

COM: center of mass.

EEG: electroencephalography.

ABC: The activities of balance confidence.

BBS: Berg Balance Scale.

TUG: Timed up and go test.

BESTest: The Balance Evaluation System Test.

APA: anticipatory postural adjustments.

MOS: Margin of stability.

FSR: feasible stability region.

PBT: perturbation-based training.

UL: upper limb.

LL: lower limb.

MS: multiple sclerosis.

MG: myasthenia gravis.

ST: single task.

DT: dual task.

RMS: root mean square.

MOCA: Montreal Cognitive Assessment Scale.

CMSA: Chedoke-McMaster Stroke Assessment.

HRV: heart rate variability.

EOF: eyes open firm surface.

ECF: Eyes close firm surface.

EOSV: Eyes open with sway referenced vision.

EOSS: Eyes open sway referenced surface.

ECSS: Eyes close sway references surface.

EOSSV: Eyes open sway referenced surface and vision.

AP: antero-posterior.

ML: medio-lateral.

HF: High frequency.

LF: Low frequency.

RMSSD: root-mean-square of differences between adjacent normal RR intervals.

Df: degree of freedom.

PFC: prefrontal cortex.

ACC: anterior cingulate cortex.

COP: center of pressure.

LOB: Loss of balance.

nLOB: No loss of balance.

SlipNorm: Computer-controlled slip-perturbation trials on firm (normal) surface.

SlipRol: Computer-controlled slip-perturbation trials on slippery surface (metallic rollers).

TripOB: Computer-controlled trip-perturbation trials with obstacles.

SlipFoam: Computer-controlled slip-perturbation trials on foam surface.

TripOBFoam: Computer-controlled trip-perturbation trials with obstacles and foam.

SlipTripFoam: Computer-controlled slip- and trip-perturbation trials on foam surface.

SlipTripOBFoam: Computer-controlled trip- and slip-perturbation trials with obstacles and foam.

NW: natural walking.

NASA TXL: Nasa Task Load Index.

BOS: base of support.

LO: Liftoff.

TD: Touch down.

FSS: Fatigue Severity scale.

AFO: Ankle foot orthosis.

RF: Rectus femoris.

AMES: Assisted Motion with Enhanced Sensation.

Chapter 1
Introduction

1.1 Background

Falls, defined as an unexpected event in which individuals come or drop down to the ground, floor, or lower level, occur at least once annually in 29% of healthy adults 65 years or older, representing a global public health concern for our aging societies (Bergen, Stevens, & Burns, 2016). On the other hand, in persons with stroke (PwS), falls correspond to a significant secondary complication with 40% of individuals experiencing a serious fall within the first year after being discharged (Persson, Hansson, & Sunnerhagen, 2011). Fall-related injuries can cause devastating outcomes such as hip fracture and traumatic head injury, requiring hospitalization and prolonged stay in a long-term care facility (Scheffer, Schuurmans, Van Dijk, Van Der Hooft, & De Rooij, 2008). Additionally, after a fall, it has been reported that a fear of falling develops in 21 to 39% of those who previously had no such fear, which may restrict their activity and affect their quality of life and participation (Scheffer et al., 2008).

Compensatory postural response has been described as one of the most important components of balance restoration after experience a loss of balance or a fall. In this context, it has been well described that changes in muscle strength, muscle coordination, and joint mobility along with impaired sensorimotor integration contribute to poor postural control (Mansfield, Wong, Bryce, Knorr, & Patterson, 2015), which ultimately impact the ability to rapidly and appropriately generate corrective muscle forces to recover from balance disturbances (Jacobs & Horak, 2007) (Shumway-Cook & Woollacott, 2007). These reactive postural responses are defined as the ability to recover from instability through a rapid postural adjustments (such as recovery steps or grasp) (Maki & McIlroy, 1997). Thus, compensatory postural responses play a major role in the recovery of balance from small perturbations (Maki & McIlroy, 1997) (Jensen, Brown, & Woollacott, 2001) and are considered the most important defense against large magnitude balance perturbations (Shumway-Cook & Woollacott, 2007).

Trip and slip like perturbations have been described as the major contributors to falls (Kelsey, Procter-Gray, Hannan, & Li, 2012). Among to this line, it has been shown that muscle weakness, gait and balance problems, poor vision, psychoactive medications, and home hazards corresponds to modifiable risk factors that are susceptible to influence in fall risk (Tinetti, Speechley, & Ginter, 1988). In the last years, it has been reported that multimodal exercise programs are effective for fall prevention (American Geriatric Society, 2001). However, recently, the recognized importance of task-specific training targeting balance recovery mechanisms and postural responses has led to interest in perturbation-based training for falls reduction among older adults and persons with neurological disorders (Bhatt, Espy, Yang, & Pai, 2011; Madehkhaksar et al., 2018; Patel & Bhatt, 2015). Perturbation-based training is an emerging paradigm based on the principle of task specificity, which consists of unexpected, repeated perturbation to simulate the accidental nature of falls (Gerards, McCrum, Mansfield, & Meijer, 2017). Specifically, after a trip, the body rotates forward while translating in the same direction. In contrast, after a slip, the body rotates backward while translation of the body continues in the forward direction. Biomechanical and behavioral studies have suggested that perturbation-based training improves responses to postural perturbations in the laboratory, reduces the risk of falling in the community, and can be retained over an extended period (Pai, Bhatt, Wang, Espy, & Pavol, 2010; Pai, Bhatt, Yang, Wang, & Kritchevsky, 2014).

On the other hand, in persons with stroke (PwS) hemiparetic gait is a persistent problem that limits mobility and imposes higher energy demands for performing basic daily activities

(Macko et al., 2001; Silver, Macko, Forrester, Goldberg, & Smith, 2000). Gait and balance deficits contribute to more than 70% of PwS sustaining a fall within 6 months (Forster & Young, 1995), leading to higher risks for hip and wrist fractures (Dennis, Lo, McDowall, & West, 2002; Kanis, Oden, & Johnell, 2001).

Limited ankle range of motion (ROM) for the affected (hemiparetic) side is a common sequela after stroke. It is caused by weakness of dorsiflexors (e.g., tibialis anterior, extensor halluces longus, and extensor digitorum longus) and stiffness of plantarflexors (e.g., gastrocnemius, soleus, tibialis posterior, flexor halluces longus, and flexor digitorum longus) (An & Won, 2016). It is well known that ankles are located close to the body's base of support and assist in controlling balance (Karakaya, Rutbil, Akpinar, Yildirim, & Karakaya, 2015). Limited ankle ROM in most of PwS impairs balance control, becoming one of the major risk factors for falls (de Haart, Geurts, Huidekoper, Fasotti, & van Limbeek, 2004). Functional gait and symmetric gait rely on ankle ROM and well controlled synergies between dorsiflexors and plantarflexors (An & Won, 2016). Additionally, normal gait requires a minimum 10° of dorsiflexion (An & Won, 2016), and plantarflexors (e.g., gastrocnemius and soleus) commonly generate forward propulsion during the push-off phase in locomotion (Liu, Anderson, Schwartz, & Delp, 2008; Neptune, Kautz, & Zajac, 2001). Due to limited ankle ROM and abnormal contraction of dorsiflexors and plantarflexors, most PwS manifest slow walking speed, reduced cadence, and shortened step length, which are common indicators of abnormal gait patterns, which in turn increase the risk of falling (An & Won, 2016; Olney & Richards, 1996). In this context, the recovery of impaired ankle motion and paretic muscle activity (e.g., dorsiflexors and plantarflexors) to improve balance control and gait performance has received attention in the last years in stroke rehabilitation (Winstein et al., 2016; Yana, Saracoglu, Emuk, & Yenilmez, 2017; Zeng, Zhu, Zhang, & Xie, 2018), and more studies in this area are needed in order to improve the efficacy of the current therapeutic strategies in stroke rehabilitation.

In addition to kinematic, biomechanics and sensorimotor functions, it has been well established that cognition and motor control interact extensively (Peterka, 2002). Along to this line, most of the situations in everyday life often involve cognitive-motor interaction, e.g. walking while talking, texting on a cell phone, or thinking about one's shopping list. Consequently, the assessment of cognitive functions such as cognitive-motor dual-tasks, attention, and mental fatigue is of great interest for gaining a better understanding of cognition/motor control interplay and for improving the diagnosis, prevention and management of cognitive impairment and falls (Kelsey et al., 2012).

1.2 Statement of the Problem

In order to perform an efficient compensatory motor response after an external perturbation or to develop anticipatory mechanism to maintain the balance control while performing a motor task, a complex integration of sensory information from the visual, vestibular, and proprioceptive systems is required (Peterka, 2002). Proper sensory integration relies on the central nervous system to depend on the optimal combination of sensory sources for balance and to reweight the sensory contributions as sensory conditions change. However, even when vestibular, visual, and somatosensory systems are intact, difficulty performing static and dynamic balance tasks under challenging surface and/or visual conditions could occur due to deficits in weighting/reweighting use of somatosensory information for balance when the sensory conditions change (Peterka, 2002). For example, standing or walking on compliant foam or irregular surfaces requires the nervous system to rely more on vestibular and visual inputs while down weighting the normal dependence upon proprioceptive inputs (Peterka, 2002). When healthy persons stand on foam with eyes closed, they away 50% more because they must rely on vestibular inputs, which have higher sensory noise than proprioceptive inputs (Van Der Kooij & Peterka, 2011). Thus, a person who cannot reweight reliance on sensory inputs properly when the sensory conditions change will be less stable than someone who can reweight sensory information for balance control. Although both perturbation-based training and therapeutic interventions, in which the motor behavior is trained under different sensory conditions, have shown promising results in improving balance control and reduce the risk of falling in population at higher risk of experience a fall, the effect of the combination of these two training strategies on postural control has not been largely reported and remain unexplored.

Another sensorimotor problem that affects general mobility and the efficacy of compensatory motor responses after experience a loss of balance is related to the neuromuscular weakness that could be seen in elderly population, but, in particular, in persons with neurological diseases. Along to this line, it has been well described that persons with stroke shows delayed paretic limb muscle onset latencies following perturbations while standing on a moveable platform compared to their non-paretic limb and to healthy older adults (Dietz & Berger, 1984; Marigold, Eng, & Inglis, 2004). In addition, ankle, knee and hip torque responses are reduced on the paretic side following platform translations (Ikai, Kamikubo, Takehara, Nishi, & Miyano, 2003), which affect significantly the efficacy of the compensatory motor responses after an external-induced postural perturbation and increase the risk of falling in this population.

Several impairment-oriented therapeutic strategies such as the use of ankle-foot orthosis, robotic assistive-movement interventions and neuromuscular electrical stimulation (NMES) appear as valid alternatives to restore muscle activation delays during gait and balance disturbance situations, in which coordinated synergies activation and interlimb coupling is needed (Cordo et al., 2013; Forster & Young, 1995). Although it has been described that the earliest phases of the reactive responses are most automatic with peripheral sensory input triggering synergies pre-set in the brainstem, whereas the later phases of the same responses are less automatic and can be modified to accomplish goals involving cortical loops (Jacobs & Horak, 2007), it is well known that reactive and volitional balance response require a healthy neuromuscular and kinematic system in order to perform efficiently the compensatory motor response triggered by the CNS (Belda-Lois et al., 2011). Hence, it is plausible to hypothesize that specific impairment-oriented interventions aimed at restoring range of motions (ROM) and paretic muscle activity could improve reactive balance as well as gait and volitional balance functions and enhance mobility and independence in PwS.

In addition to biomechanical and sensory integration functions, cognition has been largely described as an important factor for balance control and motor learning. Human upright standing is seemingly performed automatically during activities of daily living since we are able to maintain balance control during standing without giving this task specific attention. However, while upright standing was previously considered simple and effortless, today there is a consensus in that postural control for standing requires a significant allocation of cognitive resources (Woollacott & Shumway-Cook, 2002). In this line, Kerr et al. (Kerr, Condon, & McDonald, 1985) showed that spatial processing decreased more while maintaining a standing posture than while sitting, additionally, other studies showed that various cognitive task performance decreases with the increasing difficulty of postural tasks or during balance disturbances (Lajoie, Teasdale, Bard, & Fleury, 1993; Teasdale & Simoneau, 2001), and that postural sway is affected by engaging in cognitive task execution during standing, suggesting a significant interaction between postural control and attentional demand in the central nervous system (CNS) (Fraizer & Mitra, 2008; Huxhold, Li, Schmiedek, & Lindenberger, 2006). In addition, common cognitive disorders among the older adult population including secondary effects of stroke, Parkinson's disease, and dementia (including mild cognitive impairment) have been reported to increase fall risk (Fischer et al., 2017). More recently, declines in the cognitive abilities of healthy older adults have been associated with increased fall incidence (Herman, Mirelman, Giladi, Schweiger, & Hausdorff, 2010). The most common reason for mildly impaired cognitive function among older adults is mental fatigue, a failure to sustain attention for optimal performance (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2010). Consequently, mental fatigue may cause changes in gait and postural sway among older adults because both tasks require higher order neurological processes (Herman et al., 2010).

1.3 Significance of the problem

Postural control is no longer considered one system or a set of righting and equilibrium reflexes. Rather, postural control is considered a complex motor skill derived from the interaction of multiple sensorimotor and cognitive processes including biomechanical constraints, sensory integration, attention and learning (Woollacott & Shumway-Cook, 2002). In this thesis, we describe the impact of task and impairment-oriented intervention on gait, volitional and reactive balance control under different sensory conditions, and the impact of cognitive fatigue on postural sway under different sensory conditions in healthy older adults, and in persons with stroke. A better understanding of biomechanical, sensory and cognitive roles in gait and balance control may raise awareness among researchers and healthcare professionals about these important risk factor and guide future effort to integrate this knowledge into fall prevention protocols and future studies to examine the impact of divers factors on balance control in population at higher risk of falling.

1.4 Purpose and organization of the thesis

The purpose of this thesis is to describe the effect of a task-specific perturbation-based training, impairment-oriented interventions, and cognitive interventions on reactive balance control and compensatory motor response, on stability and postural sway under different sensory conditions, and on gait in healthy older adults and in persons with stroke (PwS) (Figure 1.1). This thesis is organized into five chapters. Chapter I provides an overview of the background, research question, significance of the research and concludes with the aims and hypothesis for each aim. Chapter II describe the state of the art of the topics of interest included in the four-research project presented in this thesis. Chapter III, IV, V and VI describe the series of four experiments that examined the effect of different multifactorial interventions (cognitive, sensorimotor, task and impairment-oriented interventions) on volitional and reactive balance, gait, and postural sway in healthy older adults and persons with chronic stroke.

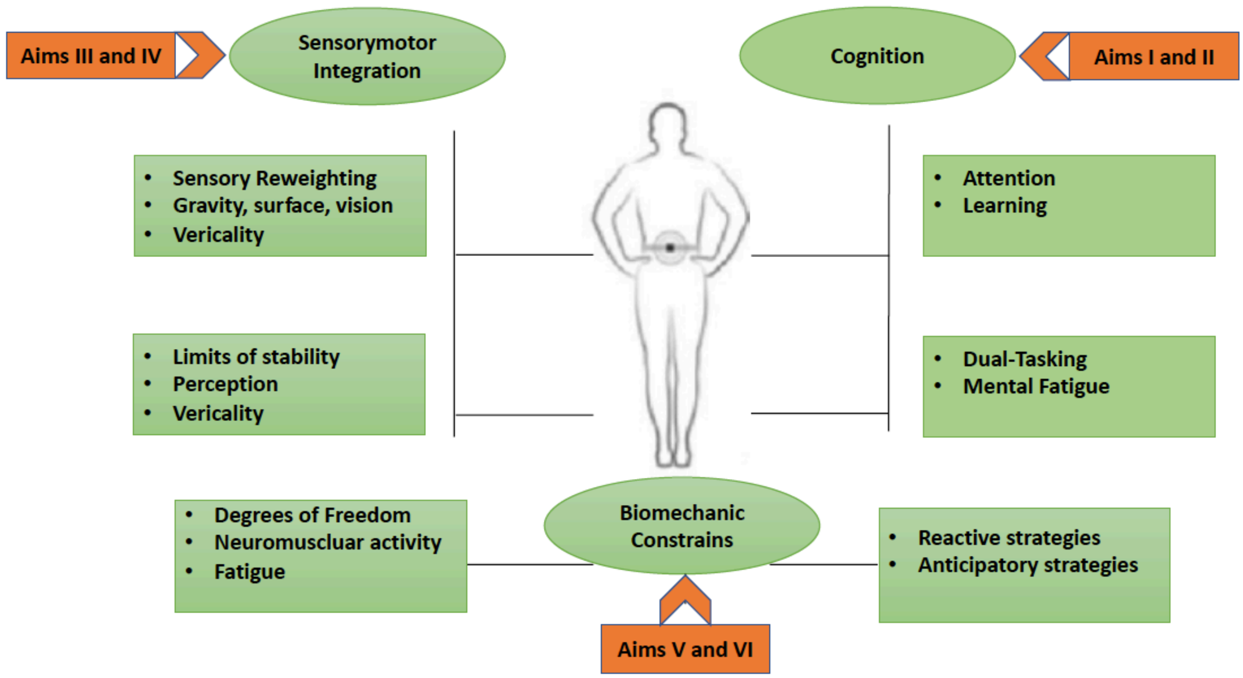

Figure 1.1 Resources required for balance control and dynamic stability. Figure 1.1 shows the principal systems involved in balance control and the relationship between cognitive, sensory-motor and biomechanics systems with the research aims of this thesis.

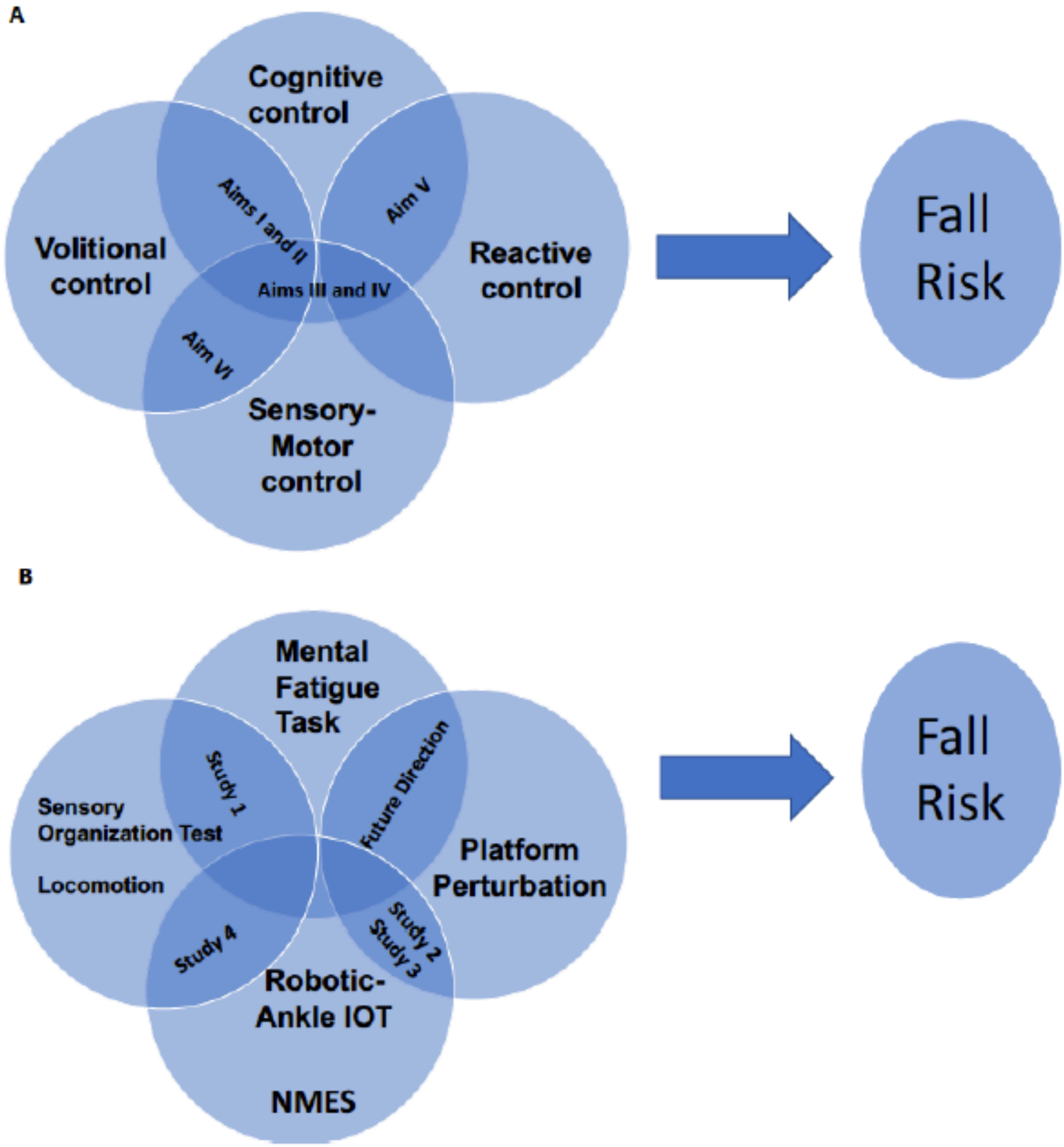

Figure 1.2 Classification of the conceptual framework according to the research aims and projects presented in this thesis. Figure A shows a scheme regarding the principal systems (Cognition, volitional and reactive balance control, and sensory motor system) involved in balance control and fall risk. Figure B shows a conceptual scheme that include the principal components of the studies presented in this thesis project related to the systems involved in balance control and fall risk. **Abbreviations:** IOT; Impairment-oriented therapy, NMES; Neuromuscular electrical stimulation

In order to address the purpose of this thesis, the following aims are proposed:

1.5 Research aims

Effect of mental fatigue on postural sway in healthy older adults and in stroke population

Aim 1: To examine the effect of mental fatigue, induced by sustained cognitive activity, on postural sway during the Sensory Organization Test (SOT) under single- and dual-task conditions.

H 1: Mental fatigue will impair balance control and increases the sway of the center of mass (COM) control during SOT specially while performing a concurrent attention-demanding cognitive task (dual-task condition) and as the SOT condition becomes more challenging among both older adults and persons with chronic stroke.

Aim 2: To compare the effect of mental fatigue on balance control during the SOT between older adults and persons with chronic stroke.

H 2: Postural sway in persons with chronic stroke will be significantly more affected by mental fatigue compared to their age-similar healthy older adults.

Assessing balance loss and stability control in older adults and in persons with chronic stroke exposed to gait perturbations: A feasibility study of a novel computer-controlled movable platform

Aim 3: To examine the feasibility of a computer-controlled movable platform to induce balance loss from perturbations under various sensory conditions in healthy older adults.

H 3: We hypothesized that this novel computer-controlled movable platform would be feasible to induce loss of balance and useful for a safe implementation of a walking perturbation protocol under different sensory conditions in healthy older adults.

Aim 4: To test the validity of this novel computer-controlled platform, comparing stability values and behavioral strategies used for the participants after perturbations between different sensory conditions included in this perturbation-based protocol, and between healthy older adults with persons with chronic stroke.

H 4: We hypothesized that the stability values would be lower and percentage of loss of balance would be higher in the conditions in which the somatosensory information is more disturbed. Additionally, we hypothesized that reactive balance control after walking perturbation would be significantly worse in persons with chronic stroke compared to healthy older adult, especially in conditions with more sensory disturbances.

Application of neuromuscular electrical stimulation on the support limb during reactive balance control in persons with stroke

Aim 5: To examine whether the application of neuromuscular electrical stimulation on the rectus femoris muscle of the support limb, triggered in synchrony with a backward and forward externally induced stance perturbation, improves stability values and reactive motor strategies in persons with chronic stroke.

H 5: We hypothesized that the application of NMES in the rectus femoris muscle of the support limb will contribute to prevent the limb collapse after a stance treadmill perturbation, improving stability values and the overall reactive response in persons with chronic stroke.

Effect of robotic-assisted ankle training on gait in stroke participants: A case series.

Aim 6: To describe the potential benefits of robotic-assisted Impairment-oriented therapy (IOT) applied to the paretic ankle of persons with stoke (PwS) on ankle impairment, and kinematic and spatiotemporal gait parameters.

H 6: We hypothesized that participants with chronic stroke would successfully complete thirty, 30-minute training sessions, 3 times per week for 10 weeks, and that the training would reduce impairments at the paretic ankle, improve interlimb coordination of the lower limbs, and improve spatiotemporal gait parameters, thereby enhancing overall gait function.

Chapter 2

State of the Art

2.1 Balance and falls, general concepts

Gait and balance disorders are commonly observed in older adulthood and in population with neurological diseases (Bergen et al., 2016; de Haart et al., 2004), which may affect their ability to live independently, safe mobility, and participation. Balance disorders may also increase fall risk (de Haart et al., 2004), contributing to injuries, hospitalization, and further loss of independence (Berg & Norman, 1996). In this context, the understanding of the sensorimotor component that are involve in balance control, and the variables that affect balance in population at higher risk of falling, such as older adults and persons with stroke, has aroused big interest in the last years in the rehabilitation science field (Horak et al, 1997; de Haart, et al 2004).

It has been well described that balance is achieved by the complex integration of multiple body systems including the vestibular, visual, auditory, motor, and higher-level cortical networks (Horak, 1997). Information from sensory systems is interpreted in the central nervous systems (CNS) based on prior experience and based on an internal body representation. Thus, a set of postural muscle synergies are activated to perform the appropriate movements to maintain balance and achieve sensorimotor functions (Macpherson & Horak, 2009).

Several studies have reported the different components that impact on balance control. In this regard, biomechanical constrains, movement and sensory strategies, body orientation in space and during movement, and cognitive aspects has been described as the main factors that contribute to the balance control and functional mobility.

2.1.1 Biomechanical constraints

It is well described that balance is not a particular position but a space determined by the size of the support base and the limitations on range of motions (ROM), muscle strength and sensory information available to detect the limits of stability, that has been defined as the area over which an individual can move their center of mass (COM) and maintain balance without changing the base of support (Pickerill & Harter, 2011). One of the most important biomechanical constraints on balance control involves the control of the COM with respect to its base of support and the corresponding limits of stability (Shumway-Cook & Woollacott, 1995).

2.1.2 Postural strategies

Three types of postural strategies have been described as the most important sensorimotor responses used to maintain and/or restore balance in a stance position (McIlroy & Maki, 1996).

- The ankle strategy, which has been described as the more efficient strategy to maintain balance in response to small amounts of sway when standing on a firm surface.
- Second, the hip strategy, in which the body exerts torque at the hips to quickly adjust the COM and keep it inside the base of support. This strategy is used when persons stand on narrow or compliant surfaces that do not allow adequate ankle torque (Horak & Kuo, 2000).
- Third, the stepping or reaching strategy which is commonly used during gait and when keeping the feet in place is not important. It has been well described that elderly individuals at risk of falling tends to use the stepping, reaching and hip strategies more than an individual with a low risk of falling (Maki, Edmondstone, & McIlroy, 2000) to maintain postural stability.

2.1.3 Sensory strategies

Although responses to postural perturbations occur faster than the firsts cued, voluntary movements, the onset of postural responses occurs at longer latencies than those of spinal stretch reflexes (Matthews, 1991), suggesting that postural responses exhibit greater potential for modification by supraspinal neural centers. Indeed, animals and humans with cortical lesions that spare the brainstem exhibit abnormal postural responses to external postural disturbances (Geurts, de Haart, van Nes, & Duysens, 2005), thereby supporting the notion that postural balance control is influenced by cortical activity. In addition, unlike stretch reflexes, postural responses involve activation of muscle synergies throughout the entire body and are also more context-specific than spinal proprioceptive reflexes (Horak & Macpherson, 2010).

2.1.4 Orientation in space

It has been well described that healthy nervous systems can automatically modify how the body is orientated in space, depending on the context and the task. Additionally, healthy individuals can identify gravitational vertical in the dark to within 0.5° degrees. Along to this line, studies have shown that perception of verticality, or upright, may have multiple neural representations (Hans-Otto Karnath, Ferber, & Dichgans, 2000). In fact, the perception of visual verticality, or the ability to align a line to gravitational vertical in the dark, is independent of the perception of postural verticality (Bisdorff, Wolsley, Anastasopoulos, Bronstein, & Gresty, 1996). Thus, the internal representation of visual, but not postural, verticality is tilted in persons with unilateral vestibular loss, whereas the internal representation of postural, but not visual, verticality is tilted in persons with hemi-neglect (a common sequel of stroke) (H-O Karnath, Fetter, & Niemeier, 1998). A tilted or inaccurate internal representation of verticality could result in an automatic postural alignment that is not aligned with gravity and, therefore, renders a person unstable.

2.1.5 Control of dynamics

Unlike quiet stance, a healthy person's COM is not within the base of foot support when walking or changing from one posture to another (Winter, MacKinnon, Ruder, & Wieman, 1993). Forward postural stability during locomotion comes from placing the swing limb under the falling COM. However, lateral stability comes from a combination of lateral trunk control and lateral placement of the feet (Bauby & Kuo, 2000). Older adults who are prone to falls tend to have larger-than-normal lateral excursions of the COM and more irregular gait spatiotemporal parameters and lateral foot placements (Prince, Corriveau, Hebert, & Winter, 1997).

2.1.6 Cognitive processing

Many cognitive resources are required to maintain balance control. Even standing quietly requires cognitive processing, as can be seen by increased reaction times to cognitive tasks in persons standing compared with persons who are sitting with support, demonstrating that the more difficult the postural task, the more cognitive processing is required (Teasdale & Simoneau, 2001). Similarly, it has been described that because the control of posture and other cognitive processing share cognitive resources, performance of postural tasks is also impaired by a secondary cognitive task (Richard Camicioli, Howieson, Lehman, & Kaye, 1997). Hence, individuals who have limited cognitive processing due to neurological disorders may use more of their available cognitive processing to control posture.

In addition, attention, mental calculation, and memory have been attributed to represent high-order cognitive functions, controlled by the cerebral cortex (Dehaene, Molko, Cohen, & Wilson, 2004; Kaiser & Lutzenberger, 2005). Thus, interactions among mental performance and balance function suggest cortical involvement in balance control. For example, in persons with stroke, it has been shown that the extent of their deficits in divided and sustained attention correlate with their fall history and balance function (Hyndman & Ashburn, 2003). In addition, in response to an imposed loss of balance, a secondary task depresses the amplitude of the perturbation-evoked cortical potentials (recorded by electroencephalography; EEG) and increases the amplitude of the perturbation-evoked postural sway (Quant, Adkin, Staines, Maki, & McIlroy, 2004). The interference between a cognitive task and perturbation-evoked potentials demonstrates that the cortical representation of sensory feedback arising from perturbed posture becomes attenuated when performing a dual-task, and that this attenuated cortical representation corresponds to impairments in the postural response (Quant et al., 2004). In addition to attention, generalized cognitive function (as assessed by clinical exams of mental calculation, orientation, and memory) correlates with balance function (as assessed by dynamic posturography or by clinical tests of balance). Similarly, it has been described that persons with dementia are at an increased risk for falls (Hauer et al., 2003). Thus, executive functions that are mediated by the cerebral cortex interact with postural control, thereby providing evidence that the activity of the cerebral cortex influences postural control.

2.2 Neurophysiology of Balance Control

Reactive responses associated to balance control, appears to be so automatic that high level cortical structures have been traditionally neglected. This earlier prevailing view was largely based, in part, on animal research. Among to this line, early reflex studies in which decerebrate cats and dogs exhibited reflex standing had led to the notion that balance is a reflex response evoked by sensory stimuli and is controlled by the neural substrates of the brain stem and spinal cord (Sherrington, 1910). Currently, behavioral evidence implicates the cerebral cortex as contributing to postural responses because they are modified by complex cognitive-motor processes thought to be mediated by the cerebral cortex, including: (1) changes in cognitive load and attention when performing concurrent tasks (dual-tasking) (Brauer et al., 2002; Maki et al., 2001; McIlroy et al., 1999), (2) changes in a subject's intentions to respond with a specific strategy (priming) (Buchanan and Horak, 2003; McIlroy and Maki, 1993), (3) learning and modification of postural responses with prior experience (learning) (Horak and Nashner, 1986; Horak et al., 1989;), and (4) with changes in initial conditions (adaptation) (Henry et al., 2001).

In addition, attention, mental calculation, and memory have been attributed to represent high-order cognitive functions, controlled by the cerebral cortex (Dehaene et al., 2004; Kaiser and Lutzenberger, 2005). Thus, interactions among mental performance and balance function suggest cortical involvement in balance control. Among to this line, in PwS, it has been shown that the extent of their deficits in divided and sustained attention correlate with their fall history and balance function (Hyndman and Ashburn, 2003). Similarly, it has been shown that in response to an imposed loss of balance, a secondary task depresses the amplitude of the perturbation-evoked cortical potentials (recorded by electroencephalography; EEG) and increases the amplitude of the perturbation-evoked postural sway (Brown et al., 1999). The interference between a cognitive task and perturbation-evoked potentials demonstrates that the cortical representation of sensory feedback arising from perturbed posture becomes attenuated when performing other tasks, and that this attenuated cortical representation corresponds to impairments in the postural response (Quant et al., 2004a). Other than attention, generalized cognitive function also (as assessed by clinical exams of mental calculation, orientation, and memory) correlates with balance function (as assessed by dynamic posturography or by clinical tests of balance), and persons with dementia are at an increased risk for falls (Buchner and Larson, 1987; Hauer et al., 2003; Kose et al., 2005). Thus, executive functions that are mediated by the cerebral cortex interact with postural control, thereby providing evidence that the activity of the cerebral cortex influences balance control. Therefore, contrary to Sherrington's postulations, the righting and balance responses are definitely not independent of voluntary or cortical influences.

2.3 Balance assessments

Maintaining balance involve the acts of controlling, achieving or restoring the COM relative to the base of support, or more generally, within the limits of stability (Pollock, Durward, Rowe, & Paul, 2000). The functional goals of the balance system include:

1. Maintenance of a specific postural alignment, such as sitting or standing,

2. Facilitation of voluntary movement, such as the movement transitions between postures, and

3. Reactions that recover balance in response to external disturbances, such as a trip, slip, or push.

The primary purposes of clinical balance assessments are targeting to identify whether or not a balance problem exists and to determine the underlying cause of the balance dysfunction. It is helpful to determine whether a balance problem exists in order to predict risk of falls and to determine effectiveness of intervention. Balance assessment tools that differentiate among types and reasons for balance problem can help direct the type of intervention for more effective management or treatment of the balance disorder. Ideally, objective, quantitative, and norm referenced tools to assess postural control in the clinic should include measures that are reflective of both the functional capabilities and quality of postural strategies, sensitive and selective for postural control abnormalities, reliable and valid, and practical (F. B. Horak, 1987).

Clinical balance assessment can be divided into three main approaches: functional assessments, a systems assessment, and quantitative assessments (Horak, 1997).

2.3.1 Functional Assessments

Functional balance tests are helpful to document balance status and changes with intervention. Functional balance tests usually rate performance on a set of motor tasks on a three to five-point scale or use a stop - watch to time how long the subject can maintain balance in a particular posture (Horak, 1997).

2.3.1.1 The Activities of Balance Confidence:

The Activities of Balance Confidence (ABC) is a useful questionnaire that evaluates self-perceived balance confidence while attempting 16 different activities of daily living. However, it has been shown to relate better to what activities people actually avoid than to future falls (Myers, Fletcher, Myers, & Sherk, 1998).

2.3.1.2 The Tinetti Balance and Gait Test (Tinetti et al., 1988):

Tinetti Balance and Gait test is one of the oldest clinical balance assessments and the widest used among older people. Tinetti balance assessment include both balance and gait measurements and has a good interrater reliability (85% agreement between raters) and excellent sensitivity (93% of fallers can be identified) (Maki, Holliday, & Topper, 1994). However, many items are difficult to assess on a 3-point scale which produce poor specificity (only 11% of no fallers were identified). Despite being widely used in clinic, the gait section is seldom used and it has ceiling effects for younger people with balance deficits (Yelnik & Bonan, 2008).

2.3.1.3 Berg Balance Scale:

In contrast to the Tinetti test, the inter-rater reliability of the Berg Balance Scale (BBS) is excellent but its sensitivity is poor to moderate (Berg, Wood-Dauphinee, & Williams, 1995). The BBS was also developed for older population, in whom a score higher than 45 was related to good balance abilities and a low risk of falling (Conradsson et al., 2007). However, a recent study showed that a change of eight points is required to reveal a clinically significant change in function among older people who are dependent in activities of daily living (Yelnik & Bonan, 2008). The BBS is easy to use and can be performed in around 20 minutes. It has also been then validated for vestibular and PwS who can walk independently (Berg et al., 1995), although with poor sensitivity (Yelnik & Bonan, 2008).

2.3.1.4 The Timed "Up and Go Test":

The Timed "Up and Go Test" (TUG) is the shortest, simplest clinical balance test, and probably the most reliable because it uses agreement in stop-watch durations rather than rating scales (Yelnik & Bonan, 2008). The TUG is widely used because of the ease with which it can be performed in the clinic (Weiss et al., 2010). In addition, the TUG test has been shown to predict risk of falls in the older adults population (Shumway-Cook & Woollacott, 2007; Whitney, Lord, & Close, 2005). The TUG duration correlates with severity of moderate-to-severe Parkinson's disease (Brusse, Zimdars, Zalewski, & Steffen, 2005), and is sensitive to therapeutic intervention in Parkinson's disease subjects but is not sensitive to early PD (Zampieri et al., 2009). Recently, the TUG has been modified to add a secondary task. The TUG cognitive consists of completing the TUG while counting backward from a number between 80 and 100 and the TUG manual consists of completing the TUG while carrying a cup of water. A score of 15 seconds on the TUG-cognitive and 14.5 seconds on the TUG-manual is associated with increased risk of falls. The clinical success of the TUG is likely related to sequencing of several important mobility skills, such as turning and sit-tostand transitions that require balance control, as well as straight-ahead gait (Salarian et al., 2009). However, the TUG suffers from the same limitations as the other functional clinical scales, since it is not possible to separate which balance and gait subcomponents are affected (Zampieri et al., 2009).

Clinical assessments of balance are easy to use, do not require expensive equipment, are usually quick to administer, and have also been shown to predict fall risk and, thus, need for therapy (Giorgetti, Harris, & Jette, 1998). However, the results obtained are subjective, show ceiling effects, are usually not responsive enough to measure small progress or deterioration in a subject's ability to balance (Blum & Korner-Bitensky, 2008). The biggest limitation of functional approach to rating balance is that it cannot specify what type of balance problem a subject has in order to direct treatment.

2.3.2 Systems Assessments

While functional clinical balance assessments are used to determine whether or not a balance problem exists, a system approach is helpful when the aim of the assessment is to determine the underlying causes of the balance deficit in order to treat it effectively (Horak, 1997). Although the previously described functional tests have demonstrated to be valid in predicting the likelihood of future falls, the tests do not help clinicians direct treatment or select therapeutic strategies (Horak, Wrisley, & Frank, 2009). One recent clinical balance test use a systems approach to characterize the underlying reasons for impaired balance control: The Balance Evaluation Systems Test (BESTest) (Horak et al., 2009).

2.3.2.1 The Balance Evaluation System Test:

The Balance Evaluation System Test (BESTest) serves as a 36-item clinical balance assessment tool, developed to assess balance impairments across six contexts of postural control: mechanical constraints, limit of stability, anticipatory postural adjustments (APAs), postural response to induced loss of balance, sensory orientation, and stability in gait.

The BESTest is the only clinical balance assessment to include tests of postural responses to external perturbations and perception of postural vertical. It also combines items from other clinical tests such as the Clinical Test of Sensory Integration for Balance, The Berg Balance Scale, the Functional Reach Test, and the Get Up and Go test (Mathias, Nayak, & Isaacs, 1986). The BESTest is unique in allowing clinicians to determine the type of balance problems which contribute to the design of therapeutic strategies and plan specific treatments for their patients. The major limitation of the BESTest is the 30 minutes needed to complete the test. Recently, a short, 10-minute version of the BESTest has been developed by eliminating redundant and insensitive items from the BESTtest (Franchignoni, Horak, Godi, Nardone, & Giordano, 2010).

2.3.3 Objective Assessments

2.3.3.1 Posturography:

Postural sway is usually quantified by characterizing and analyzing displacements of the center of foot pressure from a force plate. In the last decade, quantitative assessment of postural sway during stance have become available as clinical tools and an increasing number of physical therapists and physicians are customizing treatments for their patients based on the information from posturography (Jacobs, Horak, Tran, & Nutt, 2006; Moore, MacDougall, Gracies, Cohen, & Ondo, 2007). Recently, however, accelerometers or gyros (angular velocity sensors) placed on the trunk or head are available to measure changes in COM displacements. In that context, wearable inertial sensors provide a less expensive, more practical method for quantifying postural sway in a clinical setting. Similarly, user-friendly computer interfaces with automatic analysis are becoming more available in different clinical facilities and research centers (Bloem, Visser, & Allum, 2009).

Posturography can overcome the main drawbacks to the functional clinical balance examination such as:

- Variability in test performance (within and across different examiners).
- The subjective nature of the scoring system,
- Sensitivity to small changes (Visser, Carpenter, van der Kooij, & Bloem, 2008).

In addition, quantitative posturography can be used to evaluate therapeutic efficiency, and to predict risk of falls (Piirtola & Era, 2006). However, static posturography may not be able to detect details of the underlying pathophysiology or provide diagnostic information because, despite its excellent sensitivity, postural sway through posturography has poor specificity (Diener et al., 1986).

In contrast to static posturography, dynamic posturography involves the use of external balance perturbations or changing surface and visual conditions (Bloem et al., 2009). Postural perturbations are usually made with a movable, computerized support surface so that loss of balance is induced by sudden horizontal translations or rotations (Bloem et al., 2009).

It is also possible to use sensory perturbations to selectively manipulate one or more specific sensory input for postural control. In fact, sensory perturbations contribute clarify how each sensory system help to maintain balance control, and how well subjects can reweight the available sensory inputs as necessary to maintain balance in altered environments. A commercially available system, the Sensory Organization Test (SOT) (Neurocom International, Clackamas, Oregon), makes systematic evaluation of sensory contributions to balance control clinically feasible. In the SOT, either or both the visual surround or support surface can be “sway-referenced” so they tilt in response to body sway, thereby resulting in conditions in which visual and/or somatosensory inputs suggest that the subject is not swaying. This requires the nervous system to interpret the new sensory conditions and increase reliance on sensory inputs that are more accurately providing useful feedback about COM sway. A reduced capacity to centrally weight different sensory inputs has been identified in persons with balance deficits, like patients with Parkinson’s disease (Colnat-Coulbois et al., 2005), Alzheimer’s disease, peripheral neuropathy, or stroke (Marigold et al., 2004).

Although dynamic posturography systems give accurate data about forward-backward body sway and represent a gold-standard in measuring the motor and sensory contributions to balance control, an important disadvantage of this assessment tool is the high cost and time for training and testing, as well as space for the equipment (Visser et al., 2008). Although dynamic posturography can shed insight into the type of balance disorder, functional compensation and the likely environments leading to instability for individual subjects, it is not a diagnostic tool (Visser et al., 2008). Also, dynamic posturography is limited by not providing information about dynamic balance during gait and postural transitions.

2.3.3.2 Wearable inertial sensors:

Wearable inertial sensors consist of linear accelerometers and/or angular velocity sensors (gyroscopes) that can measure leg, arm, and torso motions while people perform clinical balance tasks or normal daily activities. For example, ambulatory gait analysis systems have been design using accelerometers on a hip belt or gyroscopes on the shanks (lower limb markers) (Sabatini, Martelloni, Scapellato, & Cavallo, 2005). Unfortunately, these systems that automatically calculate parameters of gait such as cadence, stride length, and stride velocity, do not generally evaluate postural stability of the trunk during locomotion. Postural stability during gait can be estimated, however, from time spent in double support, since persons with poor balance spend more time with both feet on the ground. However, persons with poor balance also walk more slowly and slower gait is associated with longer time spent in double support (Moe-Nilssen & Helbostad, 2004). Wearable sensors have also been used as activity monitors (Bussmann et al., 2001) or to determine time spent in various activities such as lying down, walking, sitting, and standing (Najafi et al., 2003).

Accelerometers can substitute for traditional force plate measures to characterize both postural sway during stance and anticipatory postural adjustments prior to step initiation (Mancini, et al, 2009). For example, an Xsens inertial sensor with appropriate sensitivity (MTX-49A33G15) placed on the trunk at the L5 level can wirelessly report trunk sway with respect to gravity as well as lateral trunk postural adjustments in anticipation of step initiation (Mancini, Zampieri, Carlson-Kuhta, Chiari, & Horak, 2009). Despite the potential advantages of accelerometric systems in clinical practice, they still have several drawbacks, such as the need to pre-process data and the question of how to translate sway measures into clinically understandable outcomes. However, the major limitation is that there is no consensus as to which sway-related measures should be considered. Studies have shown that root mean square (RMS) of the acceleration signal can be sensitive to test conditions (eye closure, standing on one foot), to ageing, and to history of falls. Additionally, in the last years it has been presented a new measure of postural sway, "Jerk", defined as the smoothness of the acceleration traces of the COM, which have shown to be one of the most discriminative measure to differentiate sway in patients with untreated PD compared to age-matched control subjects (Mancini et al., 2009). In the same line, Covarrubias-Escudero et al.

demonstrated an improved in Jerk values after a gait training protocol based on body-weight treadmill training in persons with chronic incomplete spinal cord injury (Covarrubias-Escudero, Rivera-Lillo, Torres-Castro, & Varas-Díaz, 2019), showing improvements in balance control after gait training in this population.

Dynamic balance during gait can also be measured during the postural transition phases of the Timed Up and Go test using inertial sensors. Salarian et al., demonstrated how a Physiologic portable 7 inertial sensors system (on chest, forearms, thighs and shanks) could quantify an extended, 6-meter, Get-Up-and-Go task to automatically identify postural transitions (sit-to-stand, turning, stand-to-sit) as well as locomotion parameters (Salarian et al., 2009), differentiating slower turn velocities, longer duration of sit-to-stand, as well as slower cadence, slower arm swing speed, more arm swing asymmetry and smaller yaw trunk rotation in untreated patients with Parkinson disease compared to patients under medication (Mancini et al., 2009).

Thus, objective measures of balance using inertial sensors systems have the potential to provide clinicians with accurate, stable, and sensitive values for longitudinal testing of balance and gait. What is needed to make quantitative measures of balance feasible for clinical practice are automatic algorithms for quantifying postural control during standardized tasks, age-corrected normative values, composite scores, and user-friendly computer interfaces so the assessments can be accomplished quickly, and data stored conveniently in electronic medical records.

2.3.3.3 Margin of stability

The margin of stability (MOS) is defined as the distance between a velocity adjusted position of the COM and the edge of an individual´s base of support at any given instant in time. It has been described that MOS is directly related to the impulse required to cause instability (A. Hof, Gazendam, & Sinke, 2005). According to this model, COM movements can be conceptualized as motions of a point mass on top of a single-segment pendulum (representing the stance leg), of which lateral oscillations passively depend on gravitational force and the body's momentum (Winter, 1995). Locomotion can thus be described as a series of controlled falls. Therefore, to understand how humans manage to exploit these falls and stay upright at the same time, understanding the control of these falling motions is needed (Hof et al., 2005).

According to the inverted pendulum model, the mediolateral MOS can be modified in two ways. First, through spatial control, i.e. through foot placement or step width regulation (Hof, 2008; Vlutters, Van Asseldonk, & Van der Kooij, 2016), as a wider step results in a larger mediolateral margin of stability. The second way to change the mediolateral margin of stability is through altering the temporal structure of stepping, i.e. modification of the single support time (Geurson, 1976). When single support time decreases, the inverted pendulum, and therefore the COM, has less time to fall to the side before foot placement. In other words, this reduces the lateral sway of the COM. Therefore, when single support time decreases, the extrapolated COM excursion is smaller, the distance between extrapolated COM and base of support increases, resulting in a larger mediolateral margin of stability. The mediolateral margin of stability can thus be increased by widening the step, but also by decreasing single support time. Multiple studies have assessed foot placement in mediolateral margin of stability regulation (Hof, 2008; Vlutters et al., 2016), indicating that foot placement after a perturbation (e.g. sideway pushes) can be predicted from the direction and magnitude of center of mass position and velocity.

2.3.3.4 Dynamic stability

The traditional view that horizontal COM positions must reside inside the BOS to guarantee maintenance of balance in standing (Borelli, 1989; Dyson, Woods, & Travers, 1986; Kuo, 1995;

Patla, Frank, & Winter, 1992) does not sufficiently define the feasible region for movement termination (Pai & Patton, 1997). The horizontal velocity of the COM should also be considered when describing the feasible movements for the balance control (Pai & Lee, 1994). For example, it is possible for the COM to be initially located outside the BOS and still be able to achieve upright standing (without falling or taking a step) if sufficient COM velocity is directed towards the BOS. Pai et al expanded the long-held concept that balance is based on one-dimensional COM position limits (i.e. the horizontal COM position has to be confined within the BOS to guarantee stable standing) to a concept based on the interaction of COM position and its velocity. Through an inverted pendulum-like two-segment sagittal model used in an optimization algorithm, Pai et al have defined the feasible stability region (FSR) with two boundaries (predicted thresholds) of all possible position-velocity combination which satisfy the task conditions: the COM arrives at a position within the BOS as its velocity vanishes, while the feet remain stationary. In other words, forward falls would be initiated if COM states (i.e. velocity and position in relative to the BOS) exceeds the upper boundary, and backward falls would be initiated if the states fell below the boundary (Pai & Patton, 1997).

2.4 Falls and perturbation-based training

Falls among older adults have been known to cause institutionalization, premature mortality, and increased use of healthcare services (Rubenstein, 2006). Approximately two-thirds of unintentional injury deaths within the older adult population are attributed to falls, and over 45% of those aged 75 years and older experience a fall each year. The prevalence of falls among the older adult population may be related to diminished neuromuscular functioning, muscle strength, peripheral sensation, vision, and cognition, which have all been associated with increased fall risk among older adults (Martin et al., 2013).

On the other hand, in persons with stroke, falls has been described as a frequent medical complication during all stage of stroke recovery, and the risk of falling and fall-related injury is more than twice as high for persons with stroke compared to similarly-aged people without stroke (Martin et al., 2013).

2.4.1 Perturbation-based training

A moderate reduction in falls risk (approximately 15–20%) have been seen in healthy older adults after exercise interventions including combinations of strength, balance and aerobic exercises (Gillespie et al., 2012). However, there is mixed evidence for whether such exercise interventions result in a significant reduction in falls incidence in frail, older adults (de Labra, Guimaraes-Pinheiro, Maseda, Lorenzo, & Millán-Calenti, 2015; Faber, Bosscher, Paw, & van Wieringen, 2006). Among the same line, there is limited evidence for falls risk reduction after such strength and balance exercise interventions alone in older adults with Parkinson's disease (Canning et al., 2015) or after a stroke (Verheyden et al., 2013). One potential reason for the inconsistency or lack of effectiveness of such general exercise interventions for falls reduction is the lack of task specificity to the recovery actions required to prevent a fall (Grabiner, Crenshaw, Hurt, Rosenblatt, & Troy, 2014). In order to recover balance after a postural disturbance, change-in-support movements (e.g. by taking compensatory steps or by grasping nearby objects for support) and counter rotations of body segments should be executed (Maki & McIlroy, 2005). Hence, training that targets such balance recovery mechanisms might be more effective than general exercise (Grabiner et al., 2014; Maki & McIlroy, 2005).

The importance of task-specific training has led to increasing interest in a new approach called perturbation-based balance training (PBT) (Maki & McIlroy, 2005; Pai & Bhatt, 2007). Perturbation-based training (PBT) is a task-specific intervention that aims to improve reactive balance control (i.e. rapid reactions to instability) after destabilizing perturbations in a safe and controlled environment. Participants are exposed to unexpected balance perturbations (e.g. treadmill accelerations, waist pulls, cable-based trips, nudge from a therapist etc.) during tasks of daily living, such as standing, walking or rising from a chair (Maki et al., 2008; Pai et al., 2010). The perturbations during PBT are unannounced in order to mimic the accidental and unexpected nature of falls in daily life (Maki et al., 2008), and ensure that the task-specific approach of PBT is in concordance with the "specificity of learning" hypothesis, which aims to demonstrate that for the learning process of a motor task, the same motor task, or at least part of this motor task, should be included in the training-learning process (Bachman, 1961). Despite the diminished reactive gait stability seen in older adults and in persons with stroke in response to a novel perturbation compared with young adults and healthy participants (Quant et al., 2004), reactive locomotor adaptation potential (the ability to adapt and improve reactive gait adjustments in a feedback-driven manner) does not appear to decline with age, and remain trainable in persons with stroke (Maki & McIlroy, 2005; Pai & Bhatt, 2007), nor does it appear to be specific to one mode (stance, sit-to-stand or gait) of locomotion (Maki et al., 2008). By capitalizing on older adults' potential for improvement by providing sufficient and specific stimuli (i.e. PBT), the reactive balance control of older adults could be improved, which might reduce their falls risk. One recent meta-analysis of randomized controlled trials using PBT indeed reported a significantly lower falls incidence in PBT groups after the interventions (Mansfield et al., 2015), with a second meta-analysis combining studies of PBT with voluntary stepping interventions also reporting reduced falls incidence in older adults and in persons with stroke (Okubo, Schoene, & Lord, 2017). However, despite this evidence, it is important to consider whether such training is effective and feasible in clinical settings, or whether such benefits are only seen in highly controlled laboratory settings. In this context, there is a consensus that more clinical applicable PBT strategies should be developed in order to contribute to the massification of this training strategy and to enhance the clinical interventions implemented in the fall prevention field.

2.5 Task- and Impairment-oriented training

Task-oriented therapies, typically based on motor learning principles, have been described as the gold standard for post-stroke rehabilitation (Winstein et al., 2016). These therapies typically emphasize the re-establishment of the PwS' independence by relearning how to perform activities of daily living or by learning compensatory movements to achieve these daily activities (Kwakkel, Kollen, & Krebs, 2008; Platz, 2004). An example of a frequently used, task-oriented approach for gait rehabilitation is treadmill training (Nadeau et al., 2013), which has been shown to increase walking speed and endurance in ambulatory PwS with gait deficits (Nadeau et al., 2013; Polese, Ada, Dean, Nascimento, & Teixeira-Salmela, 2013). However, task-oriented therapies do not focus on reducing the physical impairments resulting from the stroke, even when those impairments could affect PwS in the long-term (Nadeau et al., 2013; Polese et al., 2013).

While studies of task-oriented interventions for the lower limb (LL) have shown improvements in PwS' mobility (Mehrholz, Thomas, & Elsner, 2017; Nadeau et al., 2013; Polese et al., 2013), these studies have focused on individuals with mild-to-moderate impairment and some ambulatory ability, while excluding those with more severe impairment and minimal LL function. In contrast, treadmill training and other task-oriented therapies for non-ambulatory PwS have been found to result in no ambulatory improvement (Duncan et al., 2011; Moseley, Stark, Cameron, & Pollock, 2005), possibly because these participants were too severely impaired to regain any functional movement of the affected LL. Moseley et al. performed a meta-analysis of 15 treadmill-training clinical trials on PwS exhibiting abnormal gait patterns and concluded that there was no statistical difference in gains in walking speed between treadmill training compared to other task-oriented therapies (Moseley et al., 2005). Based on these findings, they hypothesized that, in more severely impaired PwS, impairment-oriented therapy could be a prerequisite to task-oriented therapy for restoration of functional gait.

Impairment oriented therapy (IOT) is a therapeutic strategy focusing on reducing sensorimotor impairments that interfere with normal limb movement (Cordo et al., 2013; T Platz, 2004; Thomas Platz et al., 2009). In a study investigating the relationship between specific sensorimotor impairments and gait, Kim et al. found that decreased isokinetic strength of the paretic ankle plantarflexors (i.e., increased impairment) correlated with decreased gait and stair-climbing speed in community-dwelling stroke individuals (Kim & Eng, 2003). Similarly, Lin et al. showed that dorsiflexion weakness was the single most important impairment influencing gait velocity, and that spasticity was one of the most influential impairments affecting gait symmetry (Lin, Yang, Cheng, & Wang, 2006).

The rationale for IOT directly targeting specific sensorimotor impairments is that if these impairments are sufficiently severe, they can make the performance of functional movement during rehabilitation or daily activities extremely difficult, if not impossible (Platz, 2004; Raghavan, 2007). Thus, for PwS with severe impairment, IOT represents a potentially useful restorative intervention by first minimizing fundamental physiological impairments (Thomas Platz et al., 2009), such as weakness, before higher-level functions of the limb, such as gait, are addressed. This evidence allows to hypothesize that, in more severely impaired PwS, high level functions (e.g., gait) will progress as a consequence of the restorative IOT intervention.

Impairment oriented therapy often involves assisting the patient in moving the affected limb. Assisted movement can be applied to a patient's upper limb (UL) or lower limb (LL) either with (Cordo et al., 2013) or without (Thomas Platz et al., 2009) accompanying sensory augmentation. Most assisted movement studies have thus far focused on of the ULs of stroke survivors with results indicating that the functionality of the moderately-to-mildly impaired UL can benefit from this approach (Cordo et al., 2013; Forrester, Roy, Krebs, & Macko, 2011). To date, however, few studies have addressed IOT in the LL. In one such study, Forrester et al. reported that 6 weeks of robotically assisted movement in chronic (>6 months post-stroke) PwS with mild-to-moderate impairment improved their gait biomechanics by reversing foot drop, restoring walking propulsion, increasing walking speed, and prolonging the duration of single support of the paretic leg. These results suggest that IOT could reduce ankle impairment significantly and, thereby, improve gait function in the chronic phase of stroke recovery (Forrester et al., 2011).

2.6 Mental Fatigue and balance control

Fatigue has been defined as a temporary loss of strength and energy resulting from hard physical or mental work. Community and primary care studies estimate 5%–45% of the population report fatigue as a debilitating symptom and 2%–11% report fatigue lasting at least 6 months, which has been shown to increase with age (Cullen, Kearney, & Bury, 2002).

It has been well described that fatigue is common in many chronic illnesses, including cardiovascular disease, cancer, inflammatory arthritis, and osteoarthritis (Falk, Swedberg, Gaston-Johansson, & Ekman, 2007; Ramsey-Goldman & Rothrock, 2010). In addition, it has been reported that the prevalence of fatigue is elevated in many neurologic illnesses beyond what would be expected solely on the basis of age and disability, including multiple sclerosis (MS) (Krupp, 2006), Parkinson disease (PD) (Friedman et al., 2007), traumatic brain injury (Bushnik, Englander, & Wright, 2008), myasthenia gravis (MG) (Paul, Cohen, Goldstein, & Gilchrist, 2000), stroke (Lerdal et al., 2009), and amyotrophic lateral sclerosis (Ramirez, Pimentel Piemonte, Callegaro, & Almeida Da Silva, 2008). These studies have importantly shown that fatigue is distinguishable from other related symptoms including sleepiness, depression, and apathy (Havlikova et al., 2008), and that fatigue is largely a primary symptom of neurologic illnesses and not secondary to medications, mood disorders, or sleep impairment (Havlikova et al., 2008).

2.6.1 Fatigue in stroke

A suggested definition of poststroke fatigue is a self-reported perceived lack of physical or mental energy that interferes with daily activities (Wu et al., 2017). Clinical characteristics of poststroke fatigue have been reported to include self-control and emotional instabilities, reduced mental capacity, as well as a reduction in energy needed for daily activities (Carlsson, Möller, & Blomstrand, 2003).

Poststroke fatigue is generally qualitatively different from fatigue experienced before stroke, as the former can be exacerbated by stress and physical exercise, and generally responds well to rest and adequate sleep (Annoni, Staub, Bogousslavsky, & Brioschi, 2008). This type of poststroke fatigue, commonly known as exertion fatigue, is experienced typically after intense physical exertion or use of mental effort. It is manifested in the early phase of poststroke as acute episode, with a rapid onset, short duration, and short recovery (Tseng, Billinger, Gajewski, & Kluding, 2010). The other type of poststroke fatigue is chronic fatigue, manifesting in the late phase of poststroke, and characterized by mental and psychological symptoms; the former appears with cognitively demanding tasks, whereas the latter is associated with a lack of interest or poor motivation (Staub & Bogousslavsky, 2001). Both types of poststroke fatigue are not considered mutually exclusive, although early fatigue has been reported to be more prevalent in patients after stroke, whereas late fatigue has been reported to be more prevalent in patients with other neurological chronic diseases, including multiple sclerosis (Annoni et al., 2008; Staub & Bogousslavsky, 2001).

2.6.2 Mental Fatigue

Prolonged periods of demanding cognitive activity can result in an acute state of fatigue, which has been named as mental fatigue. Some authors prefer the term cognitive fatigue to describe the psychobiological state associated with sustained cognitive activity. However, it has been recently proposed that the term mental fatigue is more appropriate, since it also includes motivational and emotional aspects associated with task accomplishment and not only cognition (Boksem & Tops, 2008).

Mental fatigue is a recurring problem in the daily life of many people and remains a challenging symptom for clinicians (Boksem & Tops, 2008). In healthy individuals it can be the consequence of prolonged and intense cognitive activity (van Iersel, Ribbers, Munneke, Borm, & Rikkert, 2007), while in persons with musculoskeletal, sensorimotor, and neurological disorders it can become a permanent condition. Mental fatigue, a component of central fatigue, has been described as a psychobiological state caused by prolonged periods of demanding cognitive activities (Marcora, Staiano, & Manning, 2009). It is characterized by feelings of tiredness and lack of energy (Marcora et al., 2009), and results in failure to maintain attention necessary for optimal performance (Holtzer et al., 2010).

2.6.3 Postural stability and executive functions

The ability to maintain an efficient balance is critical for most activities of daily living. Balance, or postural control, describes an ability to keep the body in an upright position, and when necessary, make controlled adjustments to this position (Horak, 2006). Thus, visual, vestibular, and proprioceptive organs interact to maintain balance by detecting environmental cues and translating these cues to signals that are processed by the central nervous system (Horak, 2006).

Sensorimotor tasks, such as postural control, were previously considered automatic; however, postural stability is a complex skill, dependent on coordination of the motor and sensory systems through higher order neurological processes, particularly executive functioning (Muir-Hunter et al., 2014). Executive functioning is required for planning movements, divided attention, and responding to changes within the environment (Muir-Hunter et al., 2014). Attentional demands needed to minimize sway, which increase with aging, pathology, and task difficulty (Bisson, McEwen, Lajoie, & Bilodeau, 2011). The normal aging process consists of neurodegenerative and neurochemical changes, resulting in less efficient visuospatial and sensorimotor processing (Bergamin et al., 2014), and therefore, decreased postural control. Age-related decrements in postural stability are observed during standing and when responding to environmental perturbations (Sturnieks, St George, & Lord, 2008). Numerous studies have measured balance as a function of age among healthy older adults and have found increased sway, decreased one leg standing time, and a decrease in function of the base of support (attributed to decreased toe flexor strength) to be indicative of decreased postural regulatory abilities (Bergamin et al., 2014; Bryant, Trew, Bruce, Kuisma, & Smith, 2005; Granacher, Bridenbaugh, Muehlbauer, Wehrle, & Kressig, 2011).

2.6.4 Impact of cognitive fatigue on balance and postural sway

Several studies have described that cognitive fatigue decreases concentration and attention to a given task (Holtzer et al., 2010). Although maintaining stable upright posture requires minimal attention, impaired cognitive functioning among older adults could affect balance control and stability. Along to this line, it has been well described that the regulation of postural sway requires the visual, vestibular, and proprioceptive systems; these sensory systems are weakened as a consequence of the normal aging process or a neurological disorder (Sullivan, Rose, Rohlfing, & Pfefferbaum, 2009), and, additionally, impaired as cognitive fatigue progresses (van Iersel et al., 2007).

The dual-task (DT) paradigm has been used in previous studies to investigate cognition and gait, as well as cognition and balance control through postural sway assessment. It has been well reported that postural control among older adults decreased under DT conditions (Granacher et al., 2011; van Iersel et al., 2007). Similarly, Van Iersel et al. found a cognitive DT influenced balance control among physically fit older adults directly and indirectly through decreased gait velocity, which could be a strategy to maintain balance during walking in more difficult circumstances (van Iersel et al., 2007).

Mental fatigue decreases the ability to maintain cognitive performance; therefore, a cognitively fatigued older adult might have diminished balance capabilities. Studies by Smolders et al. (2010) and Granacher et al. (2011) compared the effects of a cognitive DT on postural sway between young adults and older adults. Both studies found greater sway among the older adults, irrespective of task condition (Granacher et al., 2011; Smolders, Doumas, & Krampe, 2010). These results suggested that postural control becomes more cognitively demanding with age as a consequence of sensorimotor deficits observed among older adults (Granacher et al., 2011; Smolders et al., 2010). On the other hand, other studies explored the relationship between cognition and postural sway using clinical measures of cognitive function and balance performance tests. Along to this line, Muir-Hunter et al. found that lower scores of executive functioning among older women, obtained using the Trail-Making Test, were associated with decreased performance on the Timed Up-and-Go cognitive DT and the Fullerton Advanced Balance Scale (Muir-Hunter et al., 2014).

Additionally, structural magnetic resonance imaging (MRI) revealed brain dysmorphology among healthy older adults was associated with increased postural sway and poor balance control. Brain dysmorphology included ventricular enlargement and white matter hyperintensities, both of which contribute to weakened cognitive functioning and slower processing speed (Sullivan et al., 2009). These findings suggest that postural stability is more cognitively involved in older adults even in the absence of fatigue. Therefore, mental fatigue may present an additional challenge for older adults and persons with chronic stroke to maintain postural stability.

2.6.5 Mental fatigue and fall risk implications

Falls are a leading cause of injury and death among older adults (Jalali, Gerami, Heidarzadeh, & Soleimani, 2015). A fall is an event that results in a person coming to rest inadvertently on the ground, or other lower level (Kamińska, Brodowski, & Karakiewicz, 2015). Both, increased gait variability and increased postural sway have been shown to increase fall risk for older adults and persons with neurological disorders (LaRoche, Greenleaf, Croce, & McGaughy, 2014). Additionally, several authors have shown a relationship between cognition and fall risk among older adults. Herman et al. (2010) found that healthy older adults (no history of falls, a low comorbidity index, and good mobility upon testing) with poorer executive functioning were more likely to fall during the 2-year follow-up period (Herman et al., 2010).

In addition, it has been reported that declining cognition was associated with increased falls among older adults at risk for falling (determined by physical therapists while participants performed mobility-related activities of daily living and instrumental activities of daily living) during a 1-year follow-up period (Fischer et al., 2014). Increased fall rates were associated with participants performing an increased number of risky activities, with risky activities defined as activities that could lead to a fall based on the environment, physical, cognitive, or visual capabilities; need for assistive devices; and usual strategy or method of performance (Fischer et al., 2014). MacAulay et al. (2015) identified older adult participants as "non-fallers" or "fallers" based on fall history in the past 12 months and found that divided attention significantly impacted spatiotemporal gait parameters (e.g. stride length) (MacAulay et al., 2015). These findings support existing evidence that impaired cognitive functioning among older adults may cause greater instability and an increased fall risk.

It has been well described that mental fatigue may be considered a fall risk for older adults, irrespective of their health status. Hence, a better understanding about the mechanisms behind mental fatigue in population at higher risk of falling, and to identify in which situations mental fatigue affects balance control should be addressed in future research projects.

Chapter 3

Effect of mental fatigue on postural sway in healthy older adults and stroke population

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3.1 Introduction

Fatigue is one of the most common and disturbing symptoms in stroke and aging populations (Cumming, Packer, Kramer, & English, 2016; Eldadah, 2010; Ishii, Tanaka, & Watanabe, 2014), with negative impacts on quality of life, self-esteem, and employability(Andersen, Christensen, Kirkevold, & Johnsen, 2012; Staub & Bogousslavsky, 2001). Several authors have described fatigue as a subjective multidimensional experience, with perceptual-motor, emotional, and cognitive components associated with an intense feeling of physical and/or mental overwork, even in the absence of special effort (Boksem & Tops, 2008; Eldadah, 2010; Ishii et al., 2014). An important component of fatigue is mental fatigue, defined as a psychobiological state induced by sustained periods of demanding cognitive activity and characterized by feelings of tiredness which are common in everyday life (Boksem & Tops, 2008). Although some authors prefer to use the term cognitive fatigue to describe the psychobiological state associated with sustained cognitive activity, there is a consensus to use the term mental fatigue to include motivational and emotional aspects associated with task accomplishment (Boksem & Tops, 2008).

Evidence indicates that older adults (Eldadah, 2010), people with cognitive impairments (Wilson et al., 2007), and people with neurological disorders (Cumming et al., 2016) often experience mental fatigue to a greater extent than young adults and their healthy counterparts that can impact the performance of daily activities (Boksem & Tops, 2008). Similarly, when these populations perform dual-task paradigms, in which postural control and cognitive tasks are performed simultaneously, they experience greater cognitive-motor interference demonstrated by performance deteriorations in either motor and/or cognitive tasks (Dubost et al., 2006; Mehdizadeh et al., 2015; van Iersel et al., 2007). In this regard, studies have shown that both older adults and persons with stroke demonstrate a motor-related cognitive interference, in which they prioritize the motor tasks such as maintaining their limits of stability or gait speed controlling their postural sway while compromising performance on the cognitive tasks (Mehdizadeh et al., 2015; van Iersel et al., 2007).

While dual-task paradigm studies give us an indication of how tasks that share cognitive and motor resources might be affected when neural resources are limited, as seen in aging or damaged by pathology, the cognitive load induced in these protocols is brief (lasting only several seconds or couple minutes), which underestimate the effect of cognitive load on motor performance, explaining the predominant motor prioritization seen in older adults and in persons with stroke (Mehdizadeh et al., 2015; van Iersel et al., 2007). On the other hand, mental fatigue, caused by sustained overloading/overuse of cognitive functions, could also attenuate cognitive resource allocation for activities of daily living affecting their optimal functioning (Boksem & Tops, 2008; Ishii et al., 2014). Thus, the relationship between actual induced mental fatigue and motor performance has elicited significant interest in the field and might be important to investigate (Boksem & Tops, 2008). Recent studies have reported that mental fatigue affects cognitive performance in older adults, such as difficulties in focusing their attention, increasing their reaction time, and increasing the number of errors during standardized cognitive tasks (Kato, Endo, & Kizuka, 2009; Langner, Steinborn, Chatterjee, Sturm, & Willmes, 2010). However, mental fatigue does not only affect cognitive task performance, but also affects motor behavior. Thus, some studies have also shown that motor performance is decreased when mental fatigue is induced (R

Camicioli, Wang, Powell, Mitnitski, & Rockwood, 2007; Dubost et al., 2006; Maki & McIlroy, 1996; Schmid, Conforto, Lopez, & D'Alessio, 2007; Verghese et al., 2002). For example, Behrens et al. (2018) observed increased gait variability, assessed by coefficient of variation of speed, stride length, and stance time after mental fatigue in older adults (Behrens et al., 2018). As increased gait variability has been described as a fall-risk predictor, the authors concluded that mental fatigue could be an intrinsic risk factor for accidental falls (Behrens et al., 2018). Additionally, it has been reported that mental fatigue led to increased likelihood of slip initiation, poorer slip detection, and a more inefficient reactive recovery response to laboratory-induced slip-like perturbations in young adults (Lew & Qu, 2014), further suggesting that mental fatigue could be a risk factor for falls. However, while these studies involved challenging dynamic balance tasks, it remains to be determined if mental fatigue could also interfere with more static postural tasks which are still essential for carrying out certain simple activities of daily living. In that context, although maintaining stable upright posture requires minimal attention, it has been observed that impaired cognitive functioning among older adults and stroke population could cause balance instability and increase the risk of falls (Deschamps, Beauchet, Annweiler, Cornu, & Mignardot, 2014; Mignardot, Beauchet, Annweiler, Cornu, & Deschamps, 2014).

According to our knowledge, no study exists that has investigated the impact of mental fatigue, induced by sustained cognitive activity, on stance balance performance under different sensory conditions in older adults and in persons with chronic stroke (PwCS). In consideration to this, we assessed standing postural sway during the Sensory Organization Test (SOT), a balance test consisting of six conditions with altered sensory inputs (vision, proprioception, and vestibular), before and after a randomly assigned mental fatigue and control interventions in healthy older adults and in PwCS. Thus, the primary aim of this study was to examine the effect of mental fatigue, induced by sustained cognitive activity, on postural sway during the SOT under single- and dual-task conditions. Postural sway was assessed via root mean square (RMS) and Jerk of center of mass (COM). We hypothesized that mental fatigue impairs balance control and increases the sway of the COM control during SOT specially while performing a concurrent attention-demanding cognitive task (dual-task condition) and as the SOT condition becomes more challenging among both older adults and PwCS. The secondary aim of this study was to compare the effect of mental fatigue on postural sway during the SOT between older adults and PwCS. For this, we hypothesized that the postural sway in PwCS would be significantly more affected by mental fatigue compared to their age-similar healthy older adults.

3.2 Methods

3.2.1 Participants

Thirty healthy older adults (> 60 years old) (19 females and 11 males, age= 67.6± 7.1) were assigned either to an intervention group or to a control group (each group was composed of 15 participants). Additionally, fifteen people with hemiparetic chronic stroke (>6 months) (nine females and six males, age 63.8± 8.6) formed a second intervention group. All participants provided written informed consent and this study was approved by the Institutional Review Board in the University of Illinois at Chicago.

Healthy older adults were included if they passed a cognitive test (>26/30 on Montreal Cognitive Assessment Scale) and a mobility test (Timed Up and Go (TUG) SCORE <13.5) to ensure that these individuals were independent ambulators without balance or gait impairments. Individuals were excluded if they self-reported any neurological, musculoskeletal, or other systemic disorders that would affect the subject's postural control. On the other hand, persons with chronic stroke (PwCS) (> 6 months) were included if they were able to ambulate independently with or without an assistive device. Participants with cognitive deficits (score of < 26/30 on Montreal Cognitive Assessment Scale), speech deficits (aphasia score of > 71/100 on Mississippi Aphasia Screening Test), or presence of any other neurological, musculoskeletal, or cardiovascular condition were excluded from the study. Baseline functional status assessments, including the number of years since stroke, severity of impairment (Chedoke-McMaster Stroke Assessment), and balance testing (Berg Balance Scale, and TUG) were performed. All participant has a normal or corrected to normal vision. Demographic details and baseline clinical assessments are presented in Table 3.1.

	Older Adult Group	Stroke Group	Control Group
Age (years)	66.1±6.02	62.6±5.2	65.6±6.2
Weight (Kg.)	77.4±12.06	75.6±5.2	78.9±4.4
Hight (cms)	173.67±6	175.1±4.7	178.3±8.1
MOCA test	27.4+2.2	27.1±1.8	28.1+2.5
Impairment level			
CMSA (Leg)	-	5.18±2.01	-
CMSA (Foot)		4.6±2.1	
BBS	54.2±1	47.4±6*	54.2±1.3
TUG (s)	7.3±2.8	13.7±5.3*	7.1±1.3
Bilateral foot peripheral sensation test (number of correct answers)	91.7%	80.7%	94.3%
Paretic foot peripheral sensation test (number of correct answers)	-	66.6%	-

Table 3.1. Demographic and baseline clinical measures for study participants. Data are presented as mean ± standard deviation. For foot peripheral sensation test, a monofilament of 4.56 was used for older adults group and a monofilament of 6.65 was used for the stroke group. **Abbreviations:** MOCA, Montreal Cognitive Assessment Scale; CMSA, Chedoke-McMaster Stroke Assessment; BBS, Berg balance scale; TUG, timed up and go; Kg, kilograms; cms, centimeters S, Seconds. *p<0.05.

3.2.2 Experimental protocol

This study employed a randomized design in which thirty healthy older adults were randomized to either an experimental or a control group. Randomization was according to a random number (either 0 or 1) generated by Excel ''RAND" function. Additionally, PwCS formed a second experimental group. During the experiment, 15 healthy older adults and 15 PwCS (experimental groups) were asked to stand on a platform wearing seven MTX Xsens inertial sensors while performing the six sensory conditions included in the Sensory Organization Test (SOT) of the Balance Master under two cognitive condition (no cognitive task and serial subtractions (SS) task) before and after a cognitive fatigue task (stop-signal task for 60 min) programed by DirecRT$_{tm}$ Software. In addition, 15 healthy older adults (control group) performed the same protocol before and after watching a documentary movie for 60 minutes. Before and after each intervention heart rate variability (HRV), as a physiological indicator of mental fatigue (Garde, Laursen, Jørgensen, & Jensen, 2002), and postural sway, assessed by Jerk and RMS of COM, under single- and dual-task conditions during SOT were recorded. After each intervention, subjective fatigue, assessed by NASA Task Load Index, was conducted.

3.2.3 Cognitive fatigue and control intervention tasks

During the cognitive fatigue intervention, participants had to perform a stop-signal task (Verbruggen & Logan, 2008) for 60 minutes on a laptop computer. This task is a commonly used laboratory measure of inhibitory control that consists of presenting concurrent go and stop tasks. Participants had to press the “Space” or the “Enter” button as quickly and accurately as possible in response to the visual presentation of the letter X or Y, respectively, using their dominant hand. The stop signal consisted of a delayed tone (100 ms after the initial stimuli) presented by headphones and, when it occurred, it signaled the participants to now reverse their response and do the opposite, that is to press the “Space bar” button in response to the letter Y and the “Enter” button in response to the letter X (Figure 3.1). The percentage of correct answers were computed to monitor performance during the mental fatiguing task (Logan, Cowan, & Davis, 1984). The average of this parameter was calculated for five blocks during the stop-signal task. The control intervention consisted of watching the documentary “Earth” for 60 minutes on the same computer used for the mental fatigue task.

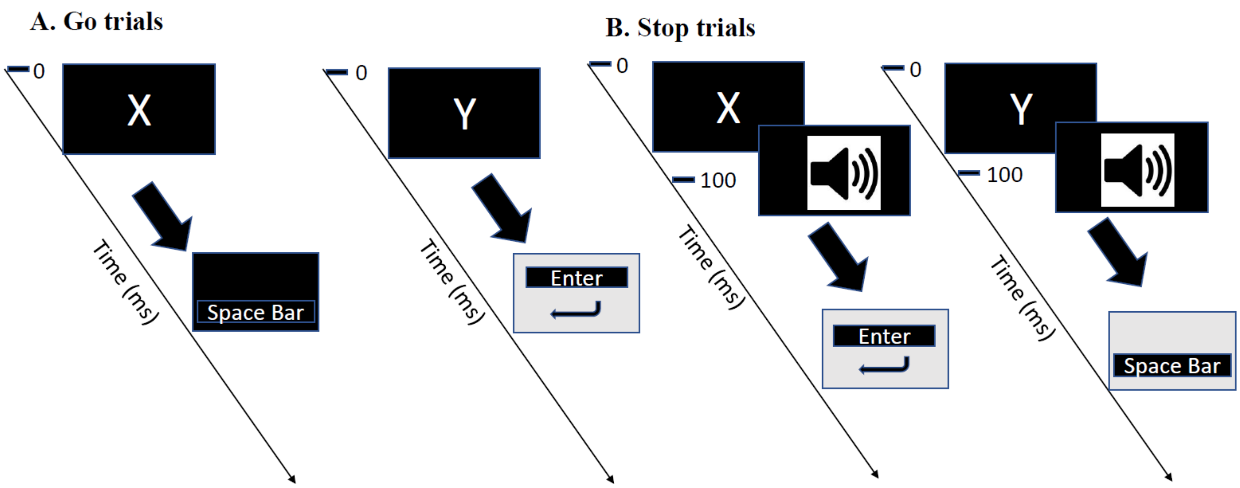

Figure 3.1. Experimental protocol for cognitive fatigue task. **A**. Participants were asked to respond to a letter X and Y pressing the “Space bar button” and “Enter button” respectively. **B**. On a subset of trials this was followed by an auditory stop signal which signaled participants to reverse their response. **Abbreviations:** ms, milliseconds.

3.2.4 Postural sway assessment

The SOT consists of six conditions designed to separate the sensory effects of vision, proprioception, and vestibular input during standing balance (Ford-Smith, Wyman, Elswick Jr, Fernandez, & Newton, 1995). The protocol consists of the following conditions: Eyes open firm surface (EOF) condition, in which participants were asked to maintain standing balance on a solid support surface with eyes open; Eyes close firm surface (ECF) condition, in which participants were asked to maintain standing balance on a solid support surface with eyes closed; Eyes open with sway referenced vision (EOSV) condition, in which participants had to maintain the standing position on solid support surface, sway referenced surround with eyes open; Eyes open sway referenced surface (EOSS) condition, in which participants had to maintain the standing balance on a sway referenced support surface with eyes open; Eyes close sway references surface (ECSS) condition, in which participants had to maintain standing balance on a sway referenced support surface with eyes closed; and Eyes open, sway referenced surface and vision (EOSSV) condition, in which participants had to maintain standing balance on a sway referenced support surface, sway referenced surround with eyes open (Ford-Smith et al., 1995; Mancini et al., 2011). It has been reported that balance control may be more sensitive to cognitive manipulations, such as cognitive load or cognitive fatigue, during challenging sensory conditions (Mehdizadeh et al., 2015). Therefore, we decided to analyze the last three conditions of the SOT, including EOSS, ECSS, and EOSSV conditions.

In order to calculate the postural sway under different sensory conditions included in SOT, participants wore MTX Xsens sensors (49A33G15, XSens, Enschede, NL) with 3-D accelerometers (±1.7g range), and 3-D gyroscopes, (±300°/s range) mounted on the posterior low back at the level of L5 (near the body center of mass), and at both lower extremities. The sensing axes were oriented along the anatomical antero-posterior (AP), medio-lateral (ML), and vertical directions.

For each trial performed during the SOT, two variables were calculated from the resultant 2-D acceleration (Acc) measured at the L5 level with respect of the base of support: 1) *root mean square acceleration (RMS)*, which quantifies the magnitude of Acc traces (Mehdizadeh et al., 2015); and 2) the resultant *Jerk of COM* value, an indicator of the smoothness of postural sway, which was computed as follows (Flash & Hogan, 1985; Mehdizadeh et al., 2015):

$$jerk = \frac{1}{2}\int_0^T \left((\frac{dAccAP}{dt})^2 + (\frac{dAccML}{dt})^2 \right)$$

where AccAP and AccML are the acceleration components measured in AP and ML direction, respectively. As a function of the time derivative of the acceleration, Jerk can be seen as a measure of the ability to control and/or to decelerate motion and as a measure of dynamic stability.

4.2.5 Dual-task protocol

In addition to the single-task balance test, outcome measures during postural sway assessment were also recorded while performing a concurrent attention-demanding cognitive task (without explicit instructions regarding prioritization). The task consisted of serial numerical subtractions, starting from a randomly selected number between 90 and 200. The results of this arithmetic task had to be recited verbally by the participants, and the cognitive interference task performance was calculated by subtracting the number of errors from the total number of subtractions. The higher the value, the better the performance (Granacher, Wolf, Wehrle, Bridenbaugh, & Kressig, 2010).

3.2.6 Psychophysiological workload

Mental fatigue is associated with the alteration of activity in multiple peripheral homeostatic pathways in response to acute stressors in older adults (Boksem & Tops, 2008). Additionally, mental fatigue and heart rate variability (HRV), particularly the parasympathetic markers derived from HRV analysis, are related to selective regions of the prefrontal cortex, basal ganglia, insula, and anterior cingulate cortex. These areas build a functional circuit called the fronto-basal ganglia circuitry which deeply involves executive functions (Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012). In this regard, the psychophysiological workload produced by the 60-minute mental fatigue and control designated task was analyzed using HRV (Garde et al., 2002). Heartbeat intervals were continuously recorded for 10 minutes in the supine position, before and immediately after the intervention (mental fatigue or control intervention). These intervals were recorded using a heart rate monitor (Polar RS800CX, Polar Electro Oy, Kempele, Finland) with a sampling rate of 1000 Hz, which wirelessly receives heart rate data from a chest strap (two-lead) worn by the participants (Mignardot et al., 2014; Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014).

The raw data were extracted from a text file stored in the polar acquisition software POLAR PRO trainer 5 (Polar Electro™, OY, Kempele, Finland) and imported into HRV analysis Kubios software (version 4.0, 2012, Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland, MATLAB) (Camm et al., 1996; Tarvainen et al., 2014).

Linear statistical measures were performed in the time and frequency domains (Camm et al., 1996). The frequency domain of HRV methods uses the power spectral density that measures how power distributes as a function of frequency. Spectral analysis of HRV signal, recorded from beat to beat variations in heart rate spectral components, which in turn differentially reflect autonomic mediators of cardiovascular variability including high-frequency (HF) and low-frequency (LF), were expressed in normalized units (nu) (Camm et al., 1996). All the frequencies were obtained using the Fast Fourier Transformation.

In the time domain analysis, the root-mean-square of differences between adjacent normal RR intervals (RMSSD) in a time interval was analyzed (Camm et al., 1996).

3.3 Results

There was no demographic (age, weight, height) differences between participants from the intervention groups and control group. Additionally, the scores of the MOCA test (28.3 $\pm$ 2.6) indicated that participants from all the groups were cognitively healthy (Table 3.1). Regarding baseline cardiovascular parameters, baseline heart rate assessment and mean of R-R intervals (time in seconds between heart beats) were not significantly different between the three groups ($p \geq 0.05$) (Table 3.2).

3.3.1 Psychophysiological workload and subjective fatigue

The two-way ANOVA for RMSSD values displayed a significant main effect of time ($F\ (1,42) = 10.873,\ p < 0.01$) and group-by-time interaction ($F\ (2,42) = 3.059,\ p = 0.048$), however, no group effect ($F\ (2,42) = 0.656,\ p = 0.524$) was observed. Similarly, for HRV HF power, we observed a significant main effect of time ($F\ (1,42) = 24.001,\ p < 0.01$), but there was no group-by-time interaction ($F\ (2,42) = 2.053,\ p = 0.141$) or group effect ($F\ (2,42) = 0.336,\ p = 0.701$) observed. Post-hoc analyses revealed that RMSSD values and HRV HF power were lower after cognitive fatigue task compared to the baseline assessment ($p < 0.05$) for the experimental older adult group and for the stroke group (both experimental groups). For the control group, no differences in RMSSD values and HRV HF power were observed between pre- and post-control tasks ($p > 0.05$) (Table 3.2).

	Older Adult Group		Stroke Group		Control Group	
Cardiovascular variables	**Baseline**	**Post intervention task**	**Baseline**	**Post intervention task**	**Baseline**	**Post intervention task**
Mean of Heart rate (beat/min)	64.6±1.7	63.4±3.5	66.3±1.1	67.1±3.1	62.8±1.8	63.6±4.7
Mean of R-R intervals	0.857±0.03	0.840±0.08	0.847±0.07	0.820±0.03	0.817±0.02	0.822±0.06
RMSSD (ms)	28.57±7.3	19.51±2.87*	27.1±16.98	22.22±9.77*	23.42±9.38	23.62±9.06
HRV HF power (n.u.)	26.04±8.69	21.7±12.8	27.49±20.7	18.9±16.45*	21.38±9.7	20.33±6.20
NASA-TLX						
Mental demand	-	68.4±22.7	-	70.9±31.9	-	13.4±24.6
Physical Demand	-	19.1±11.5	-	27.5±9.3	-	3.4±6.7
Temporal Demand	-	46.7±38.1	-	55.8±48.2	-	5.1±13.6
Performance	-	59.8±31.1	-	67.4±33.8	-	91.4±16.4
Effort	-	77.4±23.6	-	81.3±31.3	-	17.6±15.5
Frustration Level	-	39.6±37.6	-	31.3±35.6	-	4.7±4.8
Global Score	-	51.8±22.6	-	55.7±16.4	-	22.6±12.8

Table 3.2. Cardiovascular parameters pre- and post-intervention task, and NASA Task Load Index dimension scores post-intervention task. Data are presented as mean ± standard deviation. **Abbreviations:** RMSSD: root mean square of differences between adjacent normal RR intervals; HRV: Heart rate variability; HF: High frequency; ms: milliseconds; n.u.: normalized units; TLX; Task Load Index.

The one-way ANOVA for subjective fatigue revealed a significant main effect of group (*F (2,42) = 122.41, p <0.01)* for the NASA Task Load Index performed after the intervention, in which higher scores were observed in the stroke group compared to the experimental older adult group and control group ($p \leq 0.05$), and in the experimental older adults group compared to the control group ($p \leq 0.05$).

3.3.2 Balance assessments

The MANOVAs revealed that the cognitive fatigue task differentially affected postural sway (Jerk of COM and RMS) among the three groups (older adults, stroke, and control group) as indicated by a significant group by time effect. Additionally, these groups performed significantly different from each other during the SOT conditions (EOSS, ECSS, EOSSV) as indicated by a significant group by SOT condition effect. However, the type of task (single and dual task) did not have significant changes on balance control measures (jerk of COM and RMS) post-intervention. The details of these results are presented in Table 3.3 A.

Considering there was a minimal interaction effect of task (single- and dual-task) on other independent variables, the significant MANOVA's effects were resolved by performing separate repeated measures ANOVA under single and dual-task performances to determine the differences in pre vs post mental fatigue between groups for each SOT condition (Table 3.3 and 3.4).

A

Main effects and Interaction	Df (df1,df2)	Jerk of COM F Value	RMS F Value
Group effect	2,504	132.104***	23.74***
Time effect	1,504	71.175***	37.496***
Cognitive task effect (ST, DT)	1,504	16.021***	13.749***
SOT condition effect	2,504	74.751***	20.782***
Group x time effect	2,504	25.489***	11.811***
Group x Cognitive task (ST,DT)	2,504	2.533	2.249
Group x SOT condition effect	2,504	2.485*	1.833
Time x cognitive task (ST, DT)	1,504	1.277	0.453
Time x SOT condition	2,504	0.932	3.20**
Cognitive task x SOT condition	2,504	2.644	1.045
Group x time x cognitive task (ST, DT)	2,504	0.914	0.477
Group x time x SOT condition	4,504	1.273	1.872
Group x cognitive task x SOT condition	4,504	0.157	0.498
Time x cognitive task x SOT condition	2,504	0.801	0.966
Group x time x cognitive task x SOT condition	4,504	0.305	0.129

B

Main effects and Interaction		Single-task Condition		Dual-task condition	
	Df (df1,df2)	Jerk of COM F Values	RMS F Values	Jerk of COM F Values	RMS F Values
Group effect	2,126	40.641***	6.627**	65.021***	14.568**
Time effect	1,126	37.733***	30.481***	59.493***	15.760**
SOT Condition	2,126	20.618***	7.092***	39.895***	11.168**
Group x Time	2,126	12.348***	10.607***	22.970***	4.511*
Group x SOT condition	4,126	0.724	1.442	1.343	0.714
Time x SOT condition	2,126	2.375	4.90**	0.068	0.481
Group x time x SOT condition	4,126	1.438	0.994	0.73	1.324

Table 3. 3 A. MANOVA Results for Jerk and RMS of COM. **3 B.** ANOVA Results for Jerk of COM and RMS of COM during single and dual-task conditions. **Abbreviations:** COM, center of mass; RMS; root mean square; ST, single-task; DT, dual-task; SOT, Sensory Organization Test. *** $p \leq 0.001$ ** $p \leq 0.01$ * $p \leq 0.05$.

A

Main effects and Interaction		Single-Task Condition					
	Df (df1,df2)	Jerk of COM F Values			RMS of COM F Values		
		EOSS	ECSS	EOSSV	EOSS	ECSS	EOSSV
Group effect	2,42	9.79***	15.11***	15.49***	4.35*	1.179	3.184
Time effect	1,42	5.51*	21.91***	12.255***	4.053	12.15***	15.97***
Group x Time	2,42	0.81	6.42**	5.56**	4.98*	4.61*	3.90*

B

Main effects and Interaction		Dual-Task Condition					
	Df (df1,df2)	Jerk of COM F Values			RMS of COM F Values		
		EOSS	ECSS	EOSSV	EOSS	ECSS	EOSSV
Group effect	2,42	11.13***	31.22***	26.91***	9.98***	6.85**	3.44***
Time effect	1,42	27.41***	11.56***	30.58***	11.77***	6.30*	4.34*
Group x Time	2,42	4.94*	7.05**	13.43***	1.71	3.98*	2.37

Table 3.4 A. ANOVA Results for Jerk and RMS under single-task conditions during each Sensory Organization Test condition. 3.**4 B.** ANOVA Results for Jerk and RMS under dual-task conditions during each SOT condition. **Abbreviations:** COM, center of mass; RMS, root mean square; EOSS, eyes open sway referenced surface; ECSS, eyes close sway references surface; EOSSV, eyes open sway refenced surface and vision. *** $p \leq 0.001$ ** $p \leq 0.01$ * $p \leq 0.05$.

3.3.2.1 Jerk of COM during single-task assessments

Under single-task conditions, repeated measures ANOVA revealed a significant main effect of time, main effect of group, main effect of SOT conditions, and a time-by-group effect (Table 3.3 B). Overall, there was an increase in jerk as the SOT condition increased in difficulty (EOSSV>ECSS>EOSS). Resolving the time-by-group interaction for each condition revealed that for all the SOT conditions there was a significant main effect of time and group. Additionally, a time by group interaction was observed for ECSS and EOSSV conditions. The details are provided in Table 3.4a. Post-hoc analysis revealed that post-intervention, both experimental groups increased their Jerk values during ECSS and EOSSV conditions ($p \leq 0.05$). On the other hand, no pre to post changes were observed for the control group in any of the SOT conditions ($p > 0.05$) (Figure 3.2 A). Further, compared to experimental older adult group and control group, the stroke group exhibited increased Jerk values ($p \leq 0.01$) during all the SOT conditions included in the study protocol (Figure 3.2 A).

3.3.2.2 Jerk of COM during dual-task assessments

Under dual-task conditions, repeated measure ANOVA revealed a significant main effect of time, main effect of group, main effect of SOT conditions, and a time-by-group effect (Table 3.3 B). Overall, Jerk values were higher as the SOT condition increased in difficulty (EOSSV>ECSS>EOSS). Resolving the time-by-group interaction for each SOT condition, there was a significant main effect of time and group as well as a time-by-group interaction. The details are provided in Table 3.4B. Post hoc analysis revealed that post-intervention, both experimental groups increased their jerk values during EOSS, ECSS, and EOSSV conditions ($p < 0.05$). On the other hand, no pre to post changes were observed for the control group in any of the SOT conditions ($p > 0.05$) (Figure 3.2 B). Further, compared to experimental older adult group and control group, the stroke group exhibited increased jerk values ($p \leq 0.001$) during all the SOT conditions included in the study protocol (Figure 3.2 B).

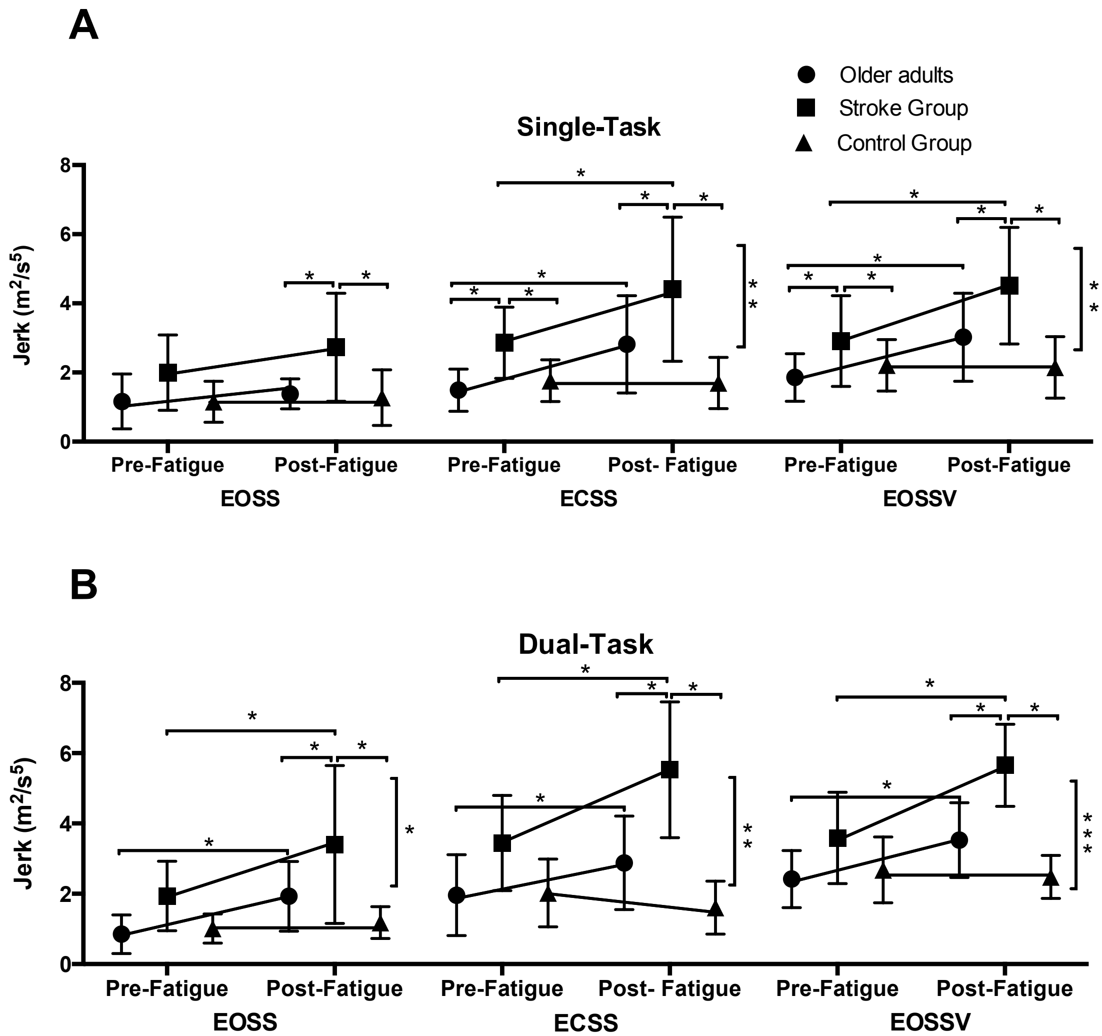

Figure 3.2. Shows the Jerk of COM values in each SOT condition for the older adults, stroke, and control groups recorded before and after the mental fatigue and control intervention, respectively, during the **A.** Single-task protocol and **B.** Dual-task protocol. Vertical bars represent time by group effect. *** $p \leq 0.001$ ** $p \leq 0.01$ * $p \leq 0.05$.

3.3.2.3 Root mean square during single-task assessments

Under single-task conditions, repeated measure ANOVA revealed a significant main effect of time, main effect of group, main effect of SOT conditions, time by group interaction, and a time by SOT condition interaction (Table 3.3 B). Overall, there was an increase in RMS as the SOT condition increased in difficulty (EOSSV>ECSS>EOSS). Resolving the time by group interaction for each SOT condition, there was a significant main effect of group and a time by group interaction for the EOSS condition. For ECSS and EOSSV conditions, there was a significant main effect of time and time x group interaction (Table 3.4 A). Post hoc analysis revealed that post-intervention, both experimental groups significantly increased their RMS compared to the baseline assessments ($p<0.05$). No pre to post changes were observed for the control group in any of the SOT conditions ($p>0.05$) (Figure 3.3 A). Further, compared to the control group, the stroke group exhibited increased RMS values during EOSS and EOSSV ($p\leq0.05$). No differences were observed between both experimental groups in any of the SOT conditions (Figure 3.3 A).

3.3.2.4 Root mean square during dual-task assessments

Under dual-task conditions, repeated measures ANOVA revealed a significant main effect of time, main effect of group, main effect of SOT conditions, and a time by group effect (Table 3.3 B). Overall, there was an increase in RMS as the SOT condition increased in difficulty (EOSSV>ECSS>EOSS). Resolving the time by group interaction for each condition, there was a significant main effect of time and group for all SOT conditions. In addition to this, a time by group interaction was observed for the ECSS condition (Table 3.4 B). Post hoc analysis revealed that post-intervention, both experimental groups increased their RMS values during the ECSS condition ($p<0.05$). No pre to post changes were observed for the control group in the ECSS SOT condition ($p>0.05$) (Figure 3.3 B). Further, compared to the control group, the stroke group exhibited an increased RMS values during ECSS and EOSSV conditions ($p\leq0.05$). No differences were observed between both experimental groups in any of the SOT conditions (Figure 3.3 A).

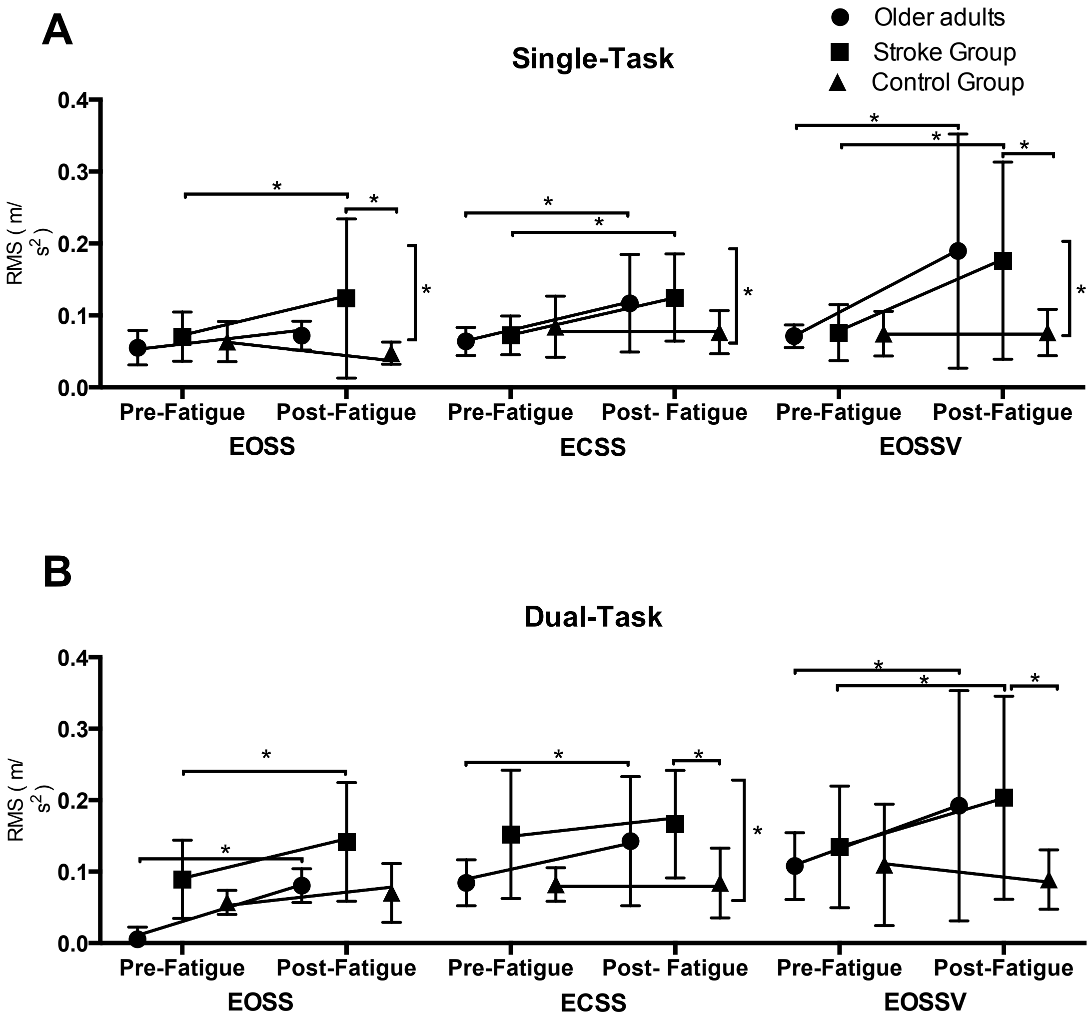

Figure 3.3. Shows the root mean squares (RMS) of COM values in each SOT condition for the older adults, stroke, and control groups recorded before and after the mental fatigue and control intervention, respectively, during the A. Single-task protocol and **B.** Dual-task protocol. *p<0.05, vertical bars represent time by group effect.

3.3.3 Performance during cognitive fatigue intervention

No differences were observed in the percentage of correct answers (p>0.05) between both experimental groups (older adults and stroke) during the stop-signal task (Table 3.5).

3.3.4 Performance during dual-task protocol

A significant main effect of time *(F (1,42) = 62.232, p<0.01)* and interaction effects of time and group *(F (2,42) = 8.233, p<0.01)* were observed for the serial subtraction task during the dual-task protocol. Post hoc analysis revealed that the cognitive performance decreased significantly in both the experimental older adult group ($p<0.01$) and the stroke group ($p<0.01$) after performing the cognitive fatigue task. No differences in the cognitive performance during dual-task protocol between pre- and post-intervention tasks were observed for the control group (Table 3.5).

	Older adults Group		Stroke Group		Control	
	Baseline	Post intervention task	Baseline	Post interventio n task	Baseline	Post interventio n task
CITP	24.01 ±7.6	14.06 ± 6.4**	21.2 ± 5.6	14.4 ± 6.8**	20.6 ± 6.4	17.8 ± 5.01
CFTP (% of correct answers)	60.94		59.64		-	
Block 1	65.3 ± 17.3		68.5 ± 12.7		-	
Block 2	61.6±27.3		61.6± 22.5		-	
Block 3	67.1±23.4		50.1±43.3		-	
Block 4	51.6±39.9		63.7± 37.2		-	
Block 5	59.1±28.6		54.3± 33.9		-	

Table 3.5. Cognitive interference task performance and Cognitive fatigue task performance of older adults' group, stroke group, and control group. The cognitive interference task performance was calculated by subtracting the number of errors from the total number of subtractions. **Abbreviations**. CITP, cognitive interference task performance; CFTP; Cognitive Fatigue Task Performance. Data are presented as mean ± standard deviation. * denotes a significant change between Pre and Post for both groups (** $p \leq 0.01$).

3.4 Discussion

The aim of the present study was to investigate the effect of mental fatigue, induced by sustained cognitive activity, on postural sway while performing the SOT under single and dual-task conditions in healthy older adults and in persons with chronic stroke (PwCS). Consistent with our hypothesis, postural sway, assessed by Jerk of COM and RMS in both AP and ML directions, increased after a 60-minute cognitive fatigue task (stop-signal task) in both healthy older adults and PwCS during SOT, with more challenging SOT conditions demonstrating greater postural sway. However, contrary to our hypothesis, the cognitive fatigue tasks did not differentially affect postural sway under single-task versus dual-task conditions. These findings suggest that mental fatigue could be seen as a potential intrinsic risk factor for balance disorders in healthy older adults and in PwCS.

4.4.1 Effect of mental fatigue on psychophysiological workload and subjective fatigue

The results indicated that mental fatigue was induced successfully in our participants as demonstrated by changes in self-reported state of fatigue and wakefulness, assessed by NASA Task Load Index. Further, this was also shown by a decrease of parasympathetic activity after the cognitive fatigue task compared to the baseline assessment, measured by time and frequency domains HRV parameters (Table 3.2), which is in line with previous studies that have used a similar computer-controlled task to provoke mental fatigue (Behrens et al., 2018; Pageaux, Marcora, & Lepers, 2013). In this regard, time domain and frequency domain HRV analyses have been widely used to investigate the cardiovascular consequences of mental work and cognitive load (Garde et al., 2002; Hjortskov et al., 2004). These show that increased levels of mental fatigue lead to a decrease of the time domain measures, as well as a decrease of the LF and HF powers, while the LF/HF ratio increases [(Garde et al., 2002; Hjortskov et al., 2004). This is postulated to occur due to a predominant decrease of the parasympathetic activity and/or a predominant increase of the sympathetic activity after cognitive workload (Garde et al., 2002; Hjortskov et al., 2004) influenced by cortical changes in brain areas related to executive functions (Thayer et al., 2012).

Brain areas related with executive control, including prefrontal cortex (PFC) and anterior cingulate cortex (ACC) have been shown to play an important role in ANS regulation. These regions inhibit the sympathoexcitatory nucleus located in subcortical areas and contribute to the balance between parasympathetic and sympathetic outflows (Hjortskov et al., 2004; Holtzer et al., 2010; Thayer et al., 2012). Under stress and workload conditions, it has been shown that PFC and ACC decrease the neural activity by reducing parasympathetic and increasing sympathetic outflow, which is interpreted as a state of autonomic hypervigilance and sympathoexcitatory activity triggered by subcortical circuits that are normally under inhibitory control of the PFC (Hjortskov et al., 2004; Holtzer et al., 2010; Thayer et al., 2012).

3.4.2 Effect of group and sensory conditions on postural sway

For older adults, baseline results (pre cognitive fatigue task) revealed an increase in Jerk and RMS of COM as the level of difficulty of the postural task increased (from EOSS to EOSSV SOT conditions). This result is consistent with previous findings which have reported that by increasing the level of postural difficulty, the amount of COP variability and postural sway increases (Marigold & Eng, 2006; Roerdink et al., 2006). It is known that the body's postural control system possesses the ability to "inhibit" poor sensory cues and "promote" reliable and consistent cues, known as sensory reweighting, which is indicated to become inefficient with aging (Mancini & Horak, 2010; Sullivan et al., 2009). In our study, as the sensory and kinesthetic information was progressively reduced or made inaccurate progressing from EOSS to EOSSV conditions, the participant was required to reweight sensory input. Inefficient sensory reweighting could have caused the individuals to experience a prolonged instability, thereby exhibiting increased postural sway. Moreover, from a physiological perspective, disturbances in visual and somatosensory information are known to increase the difficulty of postural control, resulting in decreased postural stability (Marigold & Eng, 2006). This is evidenced by the increased amount of COP variability (increased SD of velocity) and increased postural sway, previously demonstrated in older adults (Marigold & Eng, 2006; Roerdink et al., 2006). Similarly, our study showed that for ECSS and EOSSV SOT conditions, in which more than one sensory input was altered (ECSS- visual and somatosensory information were obscured; EOSSV- somatosensory and visual inputs were inaccurate), postural sway significantly increased in all groups. In this regard, maintaining balance control when sensory input is being altered challenges the postural control system to process adaptive sensory reweighting (Mancini & Horak, 2010). For example, sway-referencing the surface under a subject who has their eyes closed (ECSS) or looking at a sway-reference visual surround (EOSSV) requires a person to depend more upon vestibular inputs to control balance, which itself can be impacted by aging (Mancini & Horak, 2010). Thus, our results are in line with other studies, indicating a decreased ability of older adults to process adaptive sensory reweighting (Mancini & Horak, 2010).

Similar to the healthy older adult group, PwCS displayed decreased postural control as the sensory conditions got more challenging (Figure 3.2 and 3.3). However, our results demonstrated that, at baseline, Jerk and RMS of COM were significantly greater in PwCS compared to the healthy older adult groups for most of the SOT conditions. This could be explained because

PwCS exhibit several sensory and motor impairments which cause asymmetrical posture and weight-bearing as well as decreased muscle strength, all of which are essential factors to maintain balance control (Marigold & Eng, 2006; Marigold et al., 2004). Such impairments may further affect the ability to process adaptive sensory reweighting thereby increasing postural sway compared to healthy older adults. Along this line, PwCS have shown two-folded increases in postural sway compared to healthy older adults (Marigold et al., 2004). Findings of our study are similar to previous studies in that the dependency on visual and somatosensory information for maintaining postural control is significantly higher in PwCS relative to healthy older adults (Mancini & Horak, 2010). This could suggest that the internal representation of the postural body scheme is affected due to altered mechanisms of sensorimotor integration in supraspinal centers in PwCS. Further, the stroke-induced brain insult might affect cortical proprioceptive processing centers thus further compromising postural sway, especially when more than one sensory information source is absent (Mancini & Horak, 2010; Marigold et al., 2004).

3.4.3 Effect of mental fatigue on postural sway

As hypothesized, our results allow us to infer that mental fatigue can affect posture control in older adults and PwCS, and this effect is magnified under challenging sensory conditions (i.e., when more than one sensory input is disturbed). The effect of mental fatigue was not observed on Jerk of COM values during the EOSS condition of SOT (Fig. 3.2A), in which only one sensory input was disturbed (proprioception). However, in the ECSS condition, in which visual input is canceled and proprioceptive inputs were altered, and in the EOSSV condition, in which visual and proprioceptive inputs are manipulated and put in conflict, the effect of mental fatigue on postural sway was clearly observed in both older adults and in persons with stroke (Fig. 3.2 and Fig. 3.3).

This suggests that the control of postural sway may be more sensitive to cognitive manipulations during challenging sensory conditions compared to more stable postural tasks. In line with our findings, Mehdizadeh et al. (2015) showed that persons with stroke and healthy older adults present greater velocity of the center of pressure (COP) during a difficult compared to a simple memory task or no cognitive task while standing on foam with eyes closed (visual information canceled and somatosensory information altered) (Mehdizadeh et al., 2015). This increase in COP velocity was not observed while the same participants performed similar cognitive tasks on a firm surface with eyes open or closed (no sensory conflict), thus confirming that balance control may be more sensitive to cognitive manipulations during more demanding sensory conditions (Mehdizadeh et al., 2015).

It has been postulated that maintaining balance control requires a given amount of attentional resources which depend on the complexity of the postural task: the more challenging the postural task, the greater the required attentional resources (Lajoie et al., 1993; Palluel, Nougier, & Olivier, 2010). It has also been shown that mental fatigue decreases the activity of PFC and ACC (Holtzer et al., 2010), two of the most important brain areas involved in executive functioning, which are essential for attentional control processes during gait and balance tasks (Leone et al., 2017). Thus, impaired executive functioning could result in poor self-awareness of physical limitations and further lead to inappropriate evaluation of environmental variables, affecting subsequent motor output (Leone et al., 2017). The induction of a mental fatigue state, experienced by both experimental groups, could have an impact on the executive functioning and allocation of attentional resources required to perform the postural stability task especially under challenging environmental conditions. This could explain the differences in motor and cognitive performance observed between pre- and post-assessments in both of the intervention groups. Another plausible reason for the deterioration in postural sway after mental fatigue could be attributed to the possible structural alterations of the brain, known to occur with aging or pathology, such as a decreasing of neural connectivity in pre-frontal areas and brain dysmorphology including ventricular enlargement and white matter hyperintensities (Leone et al., 2017). Such structural changes could possibly decrease attentional capacity and cognitive processing ability while significantly increasing cognitive motor interference, especially during a state of mental fatigue. Thus, reduced attentional resources and availability of executive networks under mental fatigue combined with alterations of brain morphology (as in aging and stroke) could lead to a significant reduction of available cognitive resources that might be required for maintaining dynamic postural control, especially under challenging sensory conditions (Lajoie et al., 1993).

3.4.4 Effect of mental fatigue on dual-task

One part of our hypothesis stated that the impact of mental fatigue on postural sway in healthy older adults and in PwCS would be higher while performing a concurrent attention-demanding cognitive interference task (dual-task protocol). Although postural sway, measured by Jerk and RMS of COM, was higher during dual- compared to single-task for the three groups during the baseline assessment, Jerk and RMS values were not significantly different between single and dual-task for any of the three groups after inducing mental fatigue (Table 3.3 A and B). As it was described before, postural sway increased significantly after the cognitive fatigue task in both experimental groups. This deterioration in postural sway was similar for single and dual-task tests which allow us to infer that the effect of the induced mental fatigue was strong enough to similarly affect simple and complex balance tasks. However, another plausible explanation for this result could be accounted by the difficulty level of the dual-task paradigm implemented in this study. Previous studies have demonstrated that motor and cognitive performances are more affected during complex than simple dual-task situations (Plummer et al., 2013). As all the participants in this study were not cognitively impaired, it is possible that the dual-task protocol implemented was too simple to surface differences after the cognitive fatigue task in our participants. Finally, another possible explanation of these results is that participants could have prioritized motor instead of cognitive performance during the dual-task balance assessment after the cognitive fatigue intervention. In this regard, both the older adult and stroke groups showed a lower performance after the cognitive fatigue intervention in the serial subtraction task during the dual-task testing compared to the baseline assessment. This allows us to infer that while participants were experiencing a mental fatigue state, they prioritized the motor instead the cognitive performance during the dual-task testing.

3.5 Limitations of the study

The following limitations should be considered when interpreting the results of the current study. First, although the effect of mental fatigue on balance in older adults and in persons with stroke was demonstrated, the sample size in each group was relatively small and a large number of comparisons were performed. Second, the control group included only older adult participants. Our study did not have an explicit control group to directly compare the effect of the cognitive fatigue task versus a passive observation task in PwCS. Future studies could include a specific control group for the stroke population in order to confirm the results observed in the current protocol.

3.6 Conclusions

In conclusion, our results indicate that mental fatigue, induced by sustained cognitive activity, can impair postural sway measured during standing under varying sensory conditions performed with and without an additional cognitive task in healthy older adults and in PwCS. These results allow us to infer that the susceptibility to mental fatigue could be seen as a new intrinsic risk factor for balance disorders and/or falls in older people and in PwCS. Moreover, the potential influence of mental fatigue on balance should be considered when postural control analyses are performed in a scientific or clinical context. Future studies should investigate the underlying neural mechanisms of mental fatigue in populations with high risk of falling. In addition, future studies should focus on the dose-response relationship between the extent of mental fatigue and the increase of balance disorders and/or risk of falls in older adults and in persons with neurological diseases.

Chapter 4

Assessing balance loss and stability control in older adults and in persons with chronic stroke exposed to gait perturbations: A feasibility study of a novel computer-controlled movable platform

4.1 Introduction

Falls are a leading cause of mortality and morbidity in older adults and a significant public health issue (Bunn et al. 2014). Fall-related injuries, such as hip fractures (Terroso, Rosa, Torres-Marques, Simoes, 2014) and head injuries (Cali & Kiel, 1995; Terroso, Rosa, Torres-Marques & Simoes, 2014) are among the most serious and common medical problems experienced by older adults with approximately 28% of community-dwelling older adults experience at least one fall each year (Morley, 2002). Similarly, Falls are one of the most common medical complications after stroke (Langhorne, 2000) with an incidence of 25-37% within the first 6 months and 23-50% 6 months post stroke (Torres-Marques & Simoes, 2014). Slips and trips during walking are the most common causes of falls among older adults and persons with stroke (PwS) (Morley, 2002), which represent failures to predictively (before the perturbation) or reactively (after the perturbation) respond to environmental challenges encountered in people's daily lives (Berg, Alessio, Mills, &Tong, 1997; Kelsey, Procter-Gray, Hammam, & Li, 2012; Li et al, 2006). Therefore, there is a need to physically prepare the population at high risk of falling for situations where unexpected mechanical disturbances may occur.

It has been well described that perturbation-based balance training (PBT), defined as a task-specific intervention that aims to improve reactive balance control after destabilizing perturbations in a safe and controlled environmental (Gerards, McCurm, Mansfield, & Meijer, 2017) may reduce fall rates by 46-48% (Gerards, McCurm, Mansfield, & Meijer, 2017; Mansfield, Wong, Bryce, Knorr, & Patterson, 2015). Thus, various methods have been developed to generate balance perturbations including using a low-friction plate on a walkway (Okubo, Schoene, & Lord, 2017), treadmill accelerations (Pai, Bhatt, Yang, & Wang, 2014), motor-driven surface translations, and waist/ankle-cable pulls (McCrum, Gerards, Karamanidis, Ziilstra, & Meijer, 2017). While current PBT over-ground systems may have high ecological validity by mimicking real-life hazards realistically, the perturbations usually occur at a fixed location which leads to a loss of "unpredictability" (Bohm, Mademli, Mersmann & Arampatzis, 2015; McCrum, Gerards, Karamanidis, Ziilstra, & Meijer, 2017), and could diminish the motor learning process expected to result from these training protocols (Bohm, Mademli, Mersmann & Arampatzis, 2015). On the other hand, motor-driven surface translation devices (such as a treadmill) offer advantages since they trigger slips and/or trips by sudden platform or belt accelerations, or changes of gait speed, which reduces the level of predictability observed in the overground training, helping to focus training on reactive components of balance control (Okubo, Schoene, & Lord, 2017).

Balance control involves reactive as well as predictive processes (Patla, 2003), which are required to trigger stability mechanisms, such as modification of the base of support (BOS) and/or counter rotation of segments around the body's center of mass (COM) (Hof, 2007), to maintain postural stability during challenging conditions (e.g., perturbations) (Bierbaum, Peper, Karamanidis, Arampatzis, 2011; Marigold & Patla, 2002). Error feedback information acquired from external perturbations is used to predictively adapt the locomotion to persisting or recurring perturbations in a feedforward manner (Bierbaum, Peper, Karamanidis, Arampatzis, 2011; Marigold & Patla, 2002). Similarly, the effective use of predictive adjustments, which prepares the system for the upcoming postural threat, can reduce the consequences of the perturbation. In turn, this makes reactive responses, defined as the sensorimotor strategies performed in response to postural disturbances, easier and more successful (Bohm, Mademli, Mersmann & Arampatzis, 2015; Okubo et al, 2018; Pai, Wening, Runtz, Iqbal, & Pavol, 2003; Pavol & Pai, 2002). Along these lines, Bhatt et al reported that a smaller pre-slip propulsive impulse, coupled with flatfoot landing and increased knee flexion before slip-perturbation onset could reduce the slip-perturbation intensity and improve the following reactive responses (Bhatt, Wening & Pai, 2006). However, such gait adaptation mechanisms may be less effective when participants are exposed to different types of perturbations with high components of unpredictability, which is what usually happens before everyday falls (Okubo et al, 2018). Therefore, in order to maximize learning of "reactive" balance control (the final defense against falls in everyday life), training should regulate predictive behavior and include high components of unpredictability to PBT protocols (Okubo et al, 2018). In this context, several studies have tried to minimize the gait adaptation mechanisms during reactive balance training protocols, Bierbaum et al. introduced sufficient washout walks and regulated gait speed by light barriers when stepping on a compliant surface (e.g. trip-perturbation) (Bierbaum, Peper, Karamanidis, Arampatzis, 2011). Similarly, Bhatt et al. [21] reported mixed exposure to opposing perturbations (i.e. slip-perturbations to induce backward balance loss and trip-perturbations to induce forward balance loss) yielded reduced anticipatory shift of COM position without shortening step length before perturbations (Bhatt, Wang, Yang & Pai, 2013). Despite the positive results observed in PBT protocols including washout trials and mixed exposure to different kinds of balance perturbations, more alternatives need to be studied to increase the efficacy of interventions aimed to improve gait stability and reactive strategies after a loss of balance (LOB).

Another important factor that affects gait stability and the reactive responses after a LOB is sensory reweighting, which has been defined as the process of adjusting the sensory contributions to balance control (Assländer & Peterka, 2014). It has been well described that balance control is achieved by the complex integration and coordination of multiple sensory systems including the vestibular, visual, and proprioceptive systems (Jeka, Oie & Kiemel, 2005; Peterka, 2012). Along these lines, Peterka showed the existence of sensory reweighting by demonstrating that quantitative estimates of sensory weights changed depending on the availability of sensory information from visual or proprioceptive systems and depending on the amplitude of perturbations provided by visual surroundings or surface modifications (Peterka, 2012). Additionally, the speed of reweighting is functionally important because the failure to adjust rapidly enough can result in instability and falls when subjects either fail to generate enough corrective torque to resist gravity or generate too much torque, resulting in an overcompensated behavior (Peterka & Loughlin, 2004). It has been well described that sensory reweighting gets affected by age and in neurological diseases such as stroke (Teasdale, Stelmach, Breunig, & Meeuwsen, 1991; Woollacott, Shumway-Cook & Nashner 1986), affecting the rapid adaptation mechanisms needed to face changing environments (Allison, Kiemel & Jeka 2018). In this context, the manipulation of the sensory conditions in which a motor task is performed has been used to enhance balance training effects and to improve the variability of balance training protocols.

Clinically there have been very few offerings of balance training systems capable of inducing balance perturbations with high levels of unpredictability and modifiable sensory conditions to primarily target reactive balance control during overground walking. In this study, we utilized a novel moveable computer-controlled platform called the Surefooted Trainer, capable of inducing slip- and trip-perturbations on regular, slippery and foam surfaces with and without overlying obstacles during overground walking. The first aim of this study was to examine the feasibility of the Surefooted Trainer to induce balance loss from perturbations under various sensory conditions on healthy older adults. We hypothesized that this novel computer-controlled movable platform would be feasible to induce loss of balance and useful for a safe implementation of a walking perturbation protocol under different sensory conditions in healthy older adults. A second aim of this study was to test the discriminative validity of this novel computer-controlled platform, comparing stability values and behavioral strategies used for the participants after perturbations between different sensory conditions included in this perturbation-based protocol, and between healthy older adults with persons with chronic stroke. We hypothesized that the stability values would be lower and percentage of loss of balance would be higher in the conditions in which the somatosensory information is more disturbed. Additionally, we hypothesized that reactive balance control after walking perturbation would be significantly worse in persons with chronic stroke compared to healthy older adult, especially in conditions with more sensory disturbances.

4.2 Methods

4.2.1 Participants

Twenty-one healthy older adults (> 65 years) (12 females and 9 males), and ten community dwelling persons with chronic stroke (PwCS) (> 6 months post-stroke) (2 females and 8 males, aged 62.2±4.6) participated in this study. Healthy older adult participants were included if they passed a cognitive test (>26/30 on Montreal Cognitive Assessment Scale) and a mobility test (Six-minutes walking test, Timed Up and Go (TUG) SCORE <13.5) to ensure that they were all independent ambulators without cognitive, balance, and gait impairments. Older adults were excluded if they self-reported any neurological, musculoskeletal, or other systemic disorders that would affect the subject's postural control and/or gait functions. PwCS were included if they were able to walk independently with or without an assistive device. On the other hand, PwCS with cognitive deficits (score of < 26 on Montreal Cognitive Assessment Scale), speech deficits (aphasia score of > 71/100 on Mississippi Aphasia Screening Test), or presence of any other neurological, musculoskeletal, or cardiovascular conditions were excluded from the study. Number of years since stroke was documented. Additionally, baseline functional status assessments, including severity of impairment (Chedoke-McMaster Stroke Assessment), and balance testing (Berg Balance Scale, and TUG) were performed. All participant has a normal or corrected to normal vision. Demographic details and baseline clinical assessments are presented in Table 4.1. All participants provided written informed consent and this study was approved by the corresponding Institutional Review Board.

	Healthy older adults		Persons with chronic Stroke	
	Baseline	**Post experiment**	**Baseline**	**Post experiment**
Age (years)	66.7+4.4	-	62.2+4.6	-
Weight (Kg.)	79.1+10.05	-	77.9+10.05	-
Hight (cms)	173.67+6	-	174.43+5.2	-
MOCA test	27.7+1.8	-	26.7+1.8	-
6 MWT (m)	431.60+57	-	-	-
TUG (s)	7.3+2.2	-	10.9+5.1	-
FSS	4.1+2.4	-	4.6+2.9	-
BBS	54.2+1	-	51.6+3.6	-
Blood pressure	127+7.3/87.2+9.5		129.6+9.8/87.2+9.2	
Time since stroke	-	-	48.6+33.6	-
Bilateral foot peripheral sensation test (percentage of correct answers)	92.9%	-	81.9%	-
Paretic foot peripheral sensation test (percentage of correct answers)	-	-	67.03%	-
Motor Impairment				
CMSA (Leg)	-	-	5.3+2.2	-
CSMA (foot)	-	-	4.9+2.7	-
NASA-TLX				
Mental demand	-	3.4+6.7	-	2.6+3.7
Physical Demand	-	13.4+24.6	-	10.4+14.1
Temporal Demand	-	5.1+13.6	-	2.1+8.6
Performance	-	67.4+33.8	-	55.4+21.8
Effort	-	55.7+16.4	-	45.1+19.2
Frustration Level	-	4.7+4.8	-	9.2+3.7
Global Score	-	24.95	-	20.8

Table 4.1. Participants' demographic data and baseline cognitive and motor assessments. In addition, table 1 shows mean and standard deviations (SD) of NASA-TLX results.

4.2.2 Computer-controlled movable platform device

Participants were asked to walk over a 4 by 2 m computer-controlled movable platform, called the Surefooted Trainer, at their regular speed (Figure 4.1). Slip-perturbations and trip-perturbations were induced by the device software that moves the platform 12 inches forward and backward at 0.36 m/s seconds with an acceleration of 7.2 m/s^2. Note the platform allows two displacement settings 6 inches and 12 inches. To assess responses at the highest intensity we used 12 inches for the study.

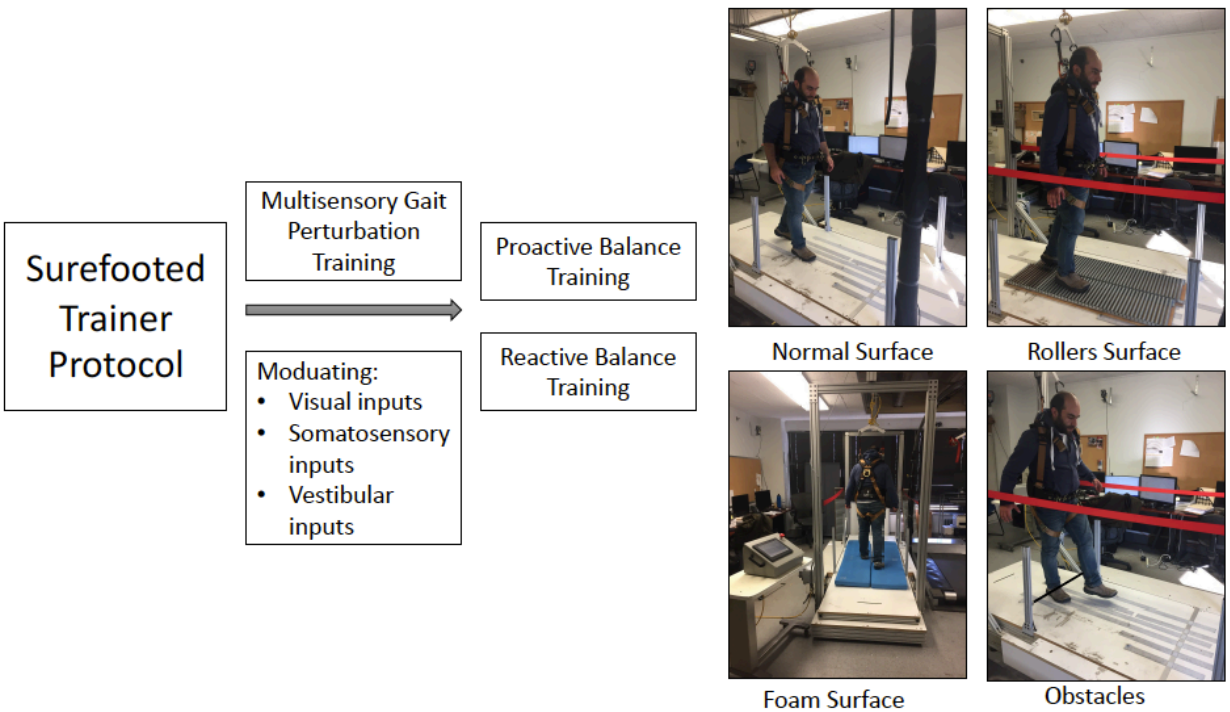

Figure 4.1. Experimental setup and conceptual framework of the Computer-controlled movable platform device (Surefooted Trainer). Forward (Slip-perturbation) and backward (Trip-perturbation) platform displacement was provided for each protocol condition.

4.2.3 Experimental protocol

Healthy older adults were asked to walk over The Surefooted Trainer under 7 different conditions wearing a safety harness. PwCS were asked to walk over the Surefooted using the normal surface (Condition 1) and over the foam surface (Condition 4). Each condition lasted for 4 minutes and consisted of 4 - 6 perturbation trials delivered. The perturbations were induced by moving the platform in forward direction (slip-perturbation) or backward direction (trip-perturbation) and were programmed to occur only when the participant was walking in the right direction and positioned near the middle of the platform.

The following training conditions were included in this study.

- Condition 1: Computer-controlled slip-perturbation trials on firm (normal) surface (SlipNorm).
- Condition 2: Computer-controlled slip-perturbation trials on slippery surface (metallic rollers) (SlipRol). Two parallel sets of 1.2 x 0.30 m metallic rollers surfaces were used in this condition. Each roller has an outside diameter of 22 mm.
- Condition 3: Computer-controlled trip-perturbation trials with obstacles (TripOB). Two elastomeric cables placed at a height of 100 mm from the platform were used in this condition. In this condition participants had to step over the obstacles two times per trial.
- Condition 4: Computer-controlled slip-perturbation trials on foam surface (SlipFoam). In this condition the whole movable platform was covered by four 1.0 x 0.4 m Airex foam balance pads 63.5 mm thick.
- Condition 5: Computer-controlled trip-perturbation trials with obstacles on foam surface (TripOBFoam). A combination of the surface conditions 3 and 4 above. Two elastomeric cables placed at a height of 100 mm from the platform were used in this condition. In this condition participants had step over the obstacles two times per trial and the whole movable platform was covered by four 1.0 x 0.4 m Airex foam balance pads 63.5 mm thick.

- Condition 6: Computer-controlled slip-perturbation and trip-perturbation trials on foam surface (SlipTripFoam). Same surface condition as 4 above with the Airex foam pads, but with slip/trip-perturbations from the moving platform.
- Condition 7: Computer-controlled slip-perturbations and trip-perturbations with obstacles on foam surface (SlipTtripOBFoam). Same surface condition as 5 above with the elastomeric cables and the Airex foam pads, but with slip/trip-perturbations from the moving platform

During the first minute of each condition, participants did not experience any perturbations (natural walking trials). During the next 3 minutes single (slip or trip-perturbation) or mixed (both slip and trip-perturbations) were experienced. In order to increase the unpredictability of each perturbation trial, the instant in which each perturbation was triggered varied from trial to trial. Participants were instructed, "when you experience a slip or trip-perturbation, try to keep walking on the platform". A one-minute break between each condition was provided. Subject's fatigue was assessed by NASA task load index score to examine the tolerability to the intervention protocol.

4.2.4 Data collection

Full body kinematics were collected using an eight-camera 3D motion capture system recording at 120 Hz (Motion Analysis, Santa Rosa, CA). A Helen Hayes marker set with 30 markers was used such that 29 markers were placed on specific bony landmarks to compute each subject's COMposition and one marker was placed on the platform to determine perturbation onset. Data from reflective markers was low pass filtered through a fourth order Butterworth filter with a cut-off frequency of 6 Hz. The weight exerted on the harness for each trial was measured by the load cell that was synchronized with the motion capture system and connected in series with the harness. Custom written algorithms in MATLAB version 2014b (The MathWorks Inc, Nactick, MA) were used to compute all kinematic variables.

4.2.5 Outcome measures

4.2.5.1 Feasibility

In order to determine the feasibility of our protocol, we evaluated the *acceptability*, *practicality*, and *safety* of our proposed intervention (Bowen et al 2009). *Acceptability* was defined as how the individuals reacted to the protocol (Bowen et al 2009). We evaluated this by examining 1) adherence to the protocol, which was defined as if participants completed the study session or not; 2) number of trip and slip-perturbations performed for each participant (to show that each participant received similar exposure to all conditions); and 3) how mentally and physically demand was the protocol for the participants through Nasa Task Load Index (NASA TXL). *Practicality* is the extent to which an intervention can be delivered when resources, time, and/or participant commitment are constrained in some way (Bowen et al 2009). In our study *practicality* was documented by the equipment, space, time (participant and personnel), and number of personnel needed. *Safety* was determined by tracking adverse events. The definition of a serious adverse event was any undesirable experience associated with the protocol that resulted in death, hospitalization, disability, or permanent damage, or required intervention to prevent permanent impairment or death. A non-serious adverse event was any incident that caused a participant to temporarily stop or halt the protocol execution (Food and Drug Administration, 2011). We anticipated non-serious adverse events of muscle soreness and nervousness based on our previous experience administering treadmill-delivered and over ground-based perturbations protocols.

4.2.5.2 Discriminative validity

Discriminative validity was measured as agreement about behavioral strategies (analyzed with direct video observation) and biomechanical outcomes (analyzed with motion capture system). During the experiment, one research member classified the behavioral strategies after each perturbation trial as loss of balance (LoB) or no loss of balance (nLoB). A backward LoB was classified as a posterior displacement of the COM with respect of the base of support accompanied by a backward step (Mourey, Manckoundia, Martin-Arveux, Tavernier-Vidal & Pfitzenmeyer, 2004). On the other hand, a forward LoB was defined as quick anterior displacement of the COM with respect of the base of support accompanied by one or multiple forward steps (Bahari, Vette, Herbert & Rouhani, 2019; Galna, Peters, Murphy & Morris, 2009). Then, after data collection, all the behavioral strategies were confirmed or modified observing the videos of each perturbation trial collected during the experiment. Finally, all the LoB and nLoB trials were compared with a commonly accepted measure of stability (the margin of stability (MOS)) (Hak, Houdijk, Beek & van Dieen, 2013; Hof, 2008) in order to corroborate that the behavioral strategies observed after each perturbation trial induced with the Surefooted Trainer were correlated with objective biomechanics outcome measures

4.2.5.3 Margin of stability

The margin of stability (MOS) is defined as the distance between a velocity adjusted position of the COM and the edge of an individual´s base of support (BOS) at any given instant in time. It has been described that MOS is directly related to the impulse required to cause instability (Hak, Houdijk, Beek & van Dieen, 2013; Hof, 2008). This variable was analyzed in 20 participants, including 383 trials, in which the time between the touch down (TD) before the perturbation and the TD after the perturbation was considered. The foot TD was identified as the instant of initial contact of the foot (heel or metatarsal marker) with the platform when the Z-trajectory of foot marker reached the baseline (i.e., position during quiet stance).

MOS was calculated using the equation below, and then normalized by BOS length:

$MOS = COM + COMv/\sqrt{(g/l)} - BOS_{max}$ Here COM indicates the position of COM, which was estimated by the sacrum marker, COMv indicates the velocity of COM in anterior-posterior direction, "l" indicates the leg length, and BOS_{max} indicates the edge of the base of support. The BOS length was calculated as foot length in single stance phase, and distance between toe of the leading foot and heel of the trailing foot in double stance phase. In this study, MOS at recovery touchdown and mean MOS were compared across four different outcomes.

4.2.5.4 Trunk angle

The trunk angle (in degrees) was computed from the position of bilateral hip and shoulder markers at compensatory step TD, with respect to vertical orientation in the sagittal plane. More negative values signified greater backward trunk extension, while more positive values signified greater forward trunk flexion at compensatory step TD. The maximum trunk angle was also calculated as the peak value from perturbation onset to recovery TD.

4.2.5.5 Step length

Recovery step length was measured as the heel-to-heel distance between the foot of the supporting limb and the recovery foot at compensatory step TD.

4.2.5.6 Behavioral results

The observed motor behaviors in response to the perturbation trials given by the computer-controlled moveable platform across the seven training conditions was classified in groups depending on whether the perturbation induced or not a fall and/or loss of balance (LOB).

Strategies classification:

- Baseline: trials in which no perturbation was induced.
- *LoB:* Loss of balance
- *nLoB:* No loss of balance

4.2.6 Statistical analysis

To examine the effect of each condition on reactive balance strategies, one-way ANOVA and post-hoc paired t-test was conducted on MOS for all conditions included in the protocol, on step length for all the slip-perturbation trials included in the protocol and on maximum trunk angle for all the trip-perturbation trials included in the protocol. To examine the effect of behavioral outcome measures on reactive balance in healthy older adults, one-way ANOVA and post hoc paired t-test was also conducted on these variables across all the outcomes (nLoB, LoB, and NW) for slip and trip-perturbations, specifically, MOS and step length was compared for slip-perturbation trials, while MOS and maximum trunk angle was compared for trip-perturbation trials. Finally, to compare behavioral and kinematic outcome measures during slip-like perturbation trials between healthy older adults and PwCS, a 2x2 repeated measures ANOVA was performed individually for the SlipNorm and SlipFoam conditions. The statistical significance was set at $p < 0.05$, and all the statistical analyses were performed using SPSS 24.00 (IBM Inc.)

4.3 Results

Twenty healthy older adults (12 females and 8 males) completed successfully this study. Additionally, ten PwCS completed condition 1 and condition 4 of the Surefooted Trainer protocol. Demographic information (age, weight, height) and baseline gait and balance abilities can be found in Table 1. Additionally, the scores of the MOCA test (28.3 ± 2.6) indicated that participants were cognitively healthy, and Fatigue Severity Scores (FSS) showed that participants' activities and lifestyle were not affected by fatigue.

4.3.1 Acceptability

20 out of the 21 participants of the healthy older adult group successfully completed the protocol including all seven conditions. Only one participant dropped out due to fear of falling caused by the characteristics of the device, in particular, arguing that the level of difficulty of SlipRol condition was too high for him. Across the entire study, participants demonstrated the ability to perform a similar number of simulated slip-perturbation repetitions (18$\pm$ 4.7) and trip-perturbation repetitions (14.4 $\pm$ 3.5). In addition, NASA TLX results indicated that the Surefooted Trainer protocol did not induce subjective mental workload in the participants (Table 4.1).

4.3.2 Practicality and Safety

Experiment protocol was successfully completed, requiring one person to operate the Surefooted Trainer and the motion camera system, and a second person to guard the participant and to interact with him in order to ensure his safety and to answer his questions (if any). The equipment size is 4m x 2 m with a high of 2.10 m which fit a standard clinical room. The time required to complete each experiment was 50 min to 1 hr., including set up of reflective markers, harness placement and testing, and calibration of the motion camera system. Regarding the safety of the protocol, there were no serious or non-serious adverse events.

4.3.3 Behavioral outcomes

A total of 283 loss of balance trials were observed during the Surefooted Trainer perturbation protocol in healthy older adults. Conditions SlipFoam (51.25%), SlipRol (80%), SlipTripFoam (77.5%), and SlipTripOBFoam (75%) were the slip-perturbation conditions in which the highest percentage of loss of balance was observed among healthy older adult participants (Table 4.2).

	Healthy older adults			**Persons with chronic Stroke**		
Study conditions	**% of trials that resulted in LoB or fall**	**N of trials that resulted in LoB or fall**	**N of perturbation trials for each condition**	**% of trials that resulted in LoB or fall**	**N of trials that resulted in LoB or fall**	**N of perturbation trials for each condition**
SlipNorm	45.8%	39	85	66.5%	26	39
SlipRol	73.7%	59	80	-	-	-
TripOB	20.6%	18	87	-	-	-
SlipFoam	80%	64	80	77.7%	31	40
TripOBFoam	26.1% 26.04+8.69	22 21.7+12.8	>0.05 84	-	-	-
SlipTripFoam (slip-perturbation trials)	77.5%	31	40	-	-	-
SlipTripOBFoam (trip-perturbation trials)	15%	6	40	-	-	-
SlipTripFoam (slip-perturbation trials)	75%	30	40	-	-	-
SlipTripOBFoam (trip-perturbation trials)	35%	14	40	-	-	-

Table 4.2. Percentage and number of loss of balance trials for each training condition. Abbreviations: SlipNorm, slip-perturbation on normal surface condition; SlipRol, slip-perturbation on rollers surface condition; SlipFoam, slip on foam surface; SlipTripFoam, slip and trip-perturbations on foam surface; SlipTripOBFoam, slip and trip-perturbations with obstacles on foam surface.

	Healthy older adults					Persons with chronic Stroke	
Participants	**LoB trials/N of perturbation trials**		**LoB trials/ N of perturbation trials**			**LoB trials/ N of perturbation trials**	**LoB trials/ N of perturbation trials**
1	1/5		5/5			2/4	4/4
2	0/5		3/4			2/4	4/4
3	3/4		5/5			3/4	4/4
4	1/4		5/5			3/4	3/4
5	4/5	26.04+8.69	4/4	21.7+12.8	>0.05	3/4	4/4
6	0/6		0/3			3/4	3/4
7	6/6		6/6			3/4	4/4
8	4/6		5/5			3/4	2/4
9	2/6		5/5			3/4	2/4
10	1/4		0/3			1/3	1/4
11	1/4		3/3			-	-
12	1/4		2/3			-	-
13	0/5		0/3			-	-
14	3/4		4/4			-	-
15	1/4		3/3			-	-
16	4/5		5/5			-	-
17	1/5		3/4			-	-
18	3/4		1/3			-	-
19	3/5		4/4			-	-
20	0/4		1/3			-	-

Table 4.3. Number of loss of balance and no loss of balance trials for each participant. Abbreviations: SlipNorm, slip-perturbation on normal surface condition; SlipFoam, slip on foam surface

4.3.4 Biomechanical outcomes

Analyzing MOS values during slip-perturbation trials of our study protocol, for condition SlipNorm there was a significant differences in MOS between NW, NLoB and LoB trials ($F(2,91) = 75.14$, $p < 0.001$). Post hoc analysis revealed that MOS values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.2 A). For condition SlipRol there was a significant differences in MOS between NW, NLoB and LoB trials ($F(2,80) = 88.68$, $p < 0.001$). Post hoc analysis revealed that MOS values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.2 B). Similarly, for condition SlipFoam there was a significant differences in MOS between NW, NLoB and LoB trials ($F(2,91) = 102.3$, $p < 0.001$). Post hoc analysis revealed that MOS values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.2 C). For slip-perturbation trials of condition SlipTripFoam there was a statistically differences in MOS between NW, NLoB and LoB trials ($F(2,79) = 67.92$, $p < 0.001$). Post hoc analysis revealed that MOS values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.2 D). And for slip-perturbation trials of condition SlipTripOBFoam there was a significant differences in MOS between NW, NLoB and LoB trials ($F(2,78) = 73.89$, $p < 0.001$). Post hoc analysis revealed that MOS values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.2 E).

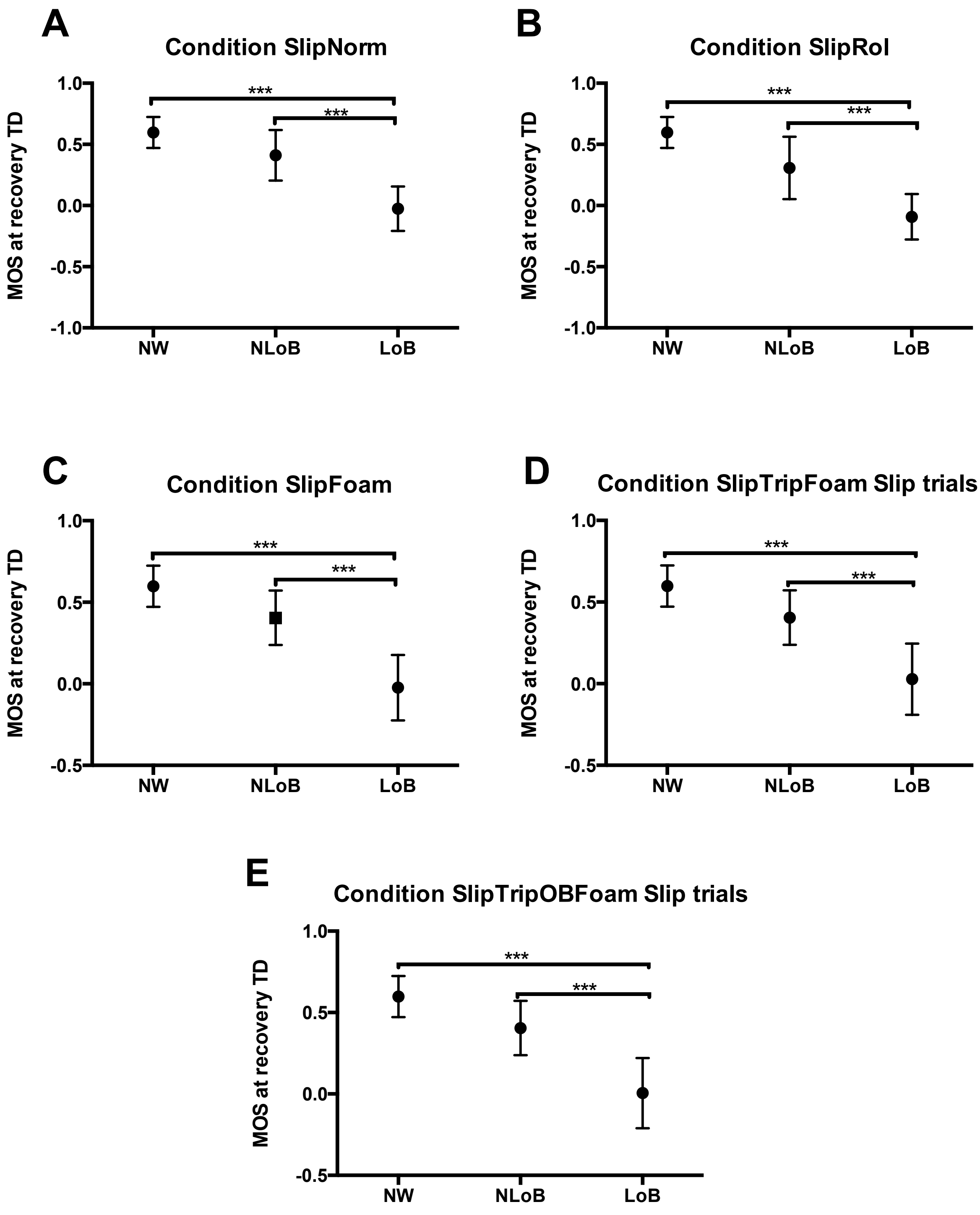

Figure 4.2 shows means and standard deviations (SD) of MOS at the recovery touch down for 20 older adults during the natural walking (NW) trials (trials in which no perturbation was induced), during the trials in which slip-perturbations did not induce a loss of balance (NLoB), and during the trials in which the slip-perturbations induced a loss of balance (LoB) in conditions SlipNorm, SlipRol, SlipFoam, and for slip-perturbation trials of conditions SlipTripFoam and SlipTripOBFoam. Abbreviations: MOS, Margin of Stability; TD, touch down; NW, natural

walking; NLoB, no loss of balance; LoB, loss of balance; SlipNorm, slip-perturbation on normal surface condition; SlipRol, slip-perturbation on rollers surface condition; SlipFoam, slip-perturbation on foam surface; SlipTripFoam, slip and trip-perturbations on foam surface; SlipTripOBFoam, slip and trip-perturbations with obstacles on foam surface. ***$p<0.001$.

Regarding MOS values during trip-perturbation trials of our study protocol, for TripOB condition there were no statistically differences between NW, NLoB and LoB trials ($F(2,83) = 4.38$, $p = 0.062$) (Figure 4.3 A). For TripOBFoam condition there were no differences in MOS between NW, NLoB and LoB trials ($F(2,91) = 5.018$, $p < 0.056$) (Figure 4.3 B). For trip-perturbation trials of condition SlipTripFoam there were no differences in MOS between NW, NLoB and LoB trials ($F(2,74) = 1.368$, $p = 0.26$) (Figure 4.3 C). And for trip-perturbation trials of condition SlipTripOBFoam there were no differences in MOS between NW, NLoB and LoB trials ($F(2,82) = 0.8279$, $p = 0.44$) (Figure 4.3 D).

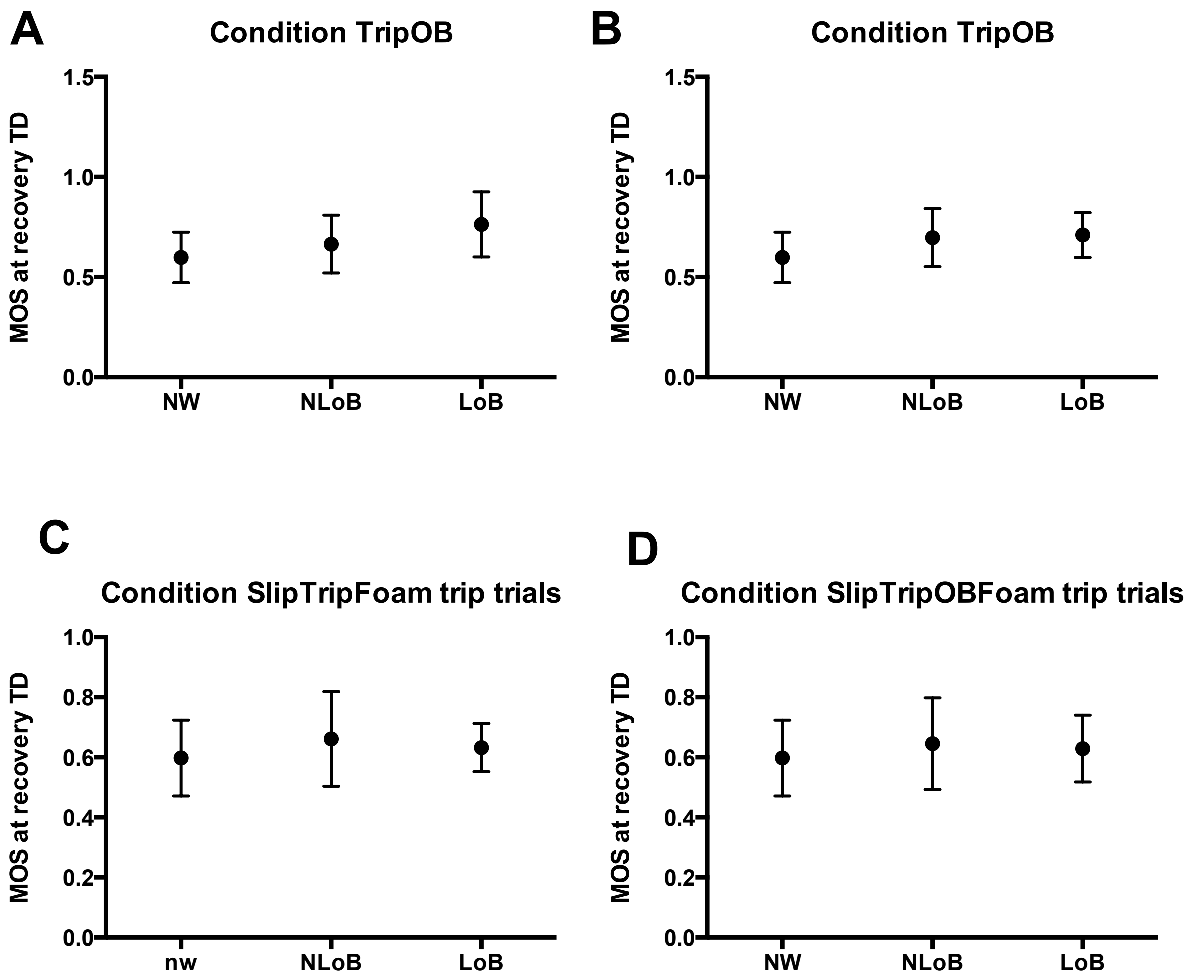

Figure 4.3 shows means and standard deviations (SD) of MOS at the recovery touch down for 20 older adults during the natural walking (NW) trials (trials in which no perturbation was induced), during the trials in which **trip-perturbations** did not induce a loss of balance (NLoB), and during the trials in which the **trip-perturbations** induced a loss of balance (LoB) in conditions TripOB and TripOBFoam, and for trip-perturbation trials of conditions SlipTripFoam and SlipTripOBFoam. Abbreviations: MOS, Margin of Stability; TD, touch down; NW, natural walking; NLoB, no loss of balance; LoB, loss of balance. TripOB, Trip-perturbations with obstacles; TripOBFoam, Trip-perturbations with obstacles on foam surface; SlipTripFoam, slip and trip-perturbations on foam surface; SlipTripOBFoam, slip and trip-perturbations with obstacles on foam surface.

For step length at the recovery step after slip-perturbations, in condition SlipNorm there was a significant differences between NW, NLoB and LoB trials ($F(2,91) = 83.72$, $p < 0.001$). Post hoc analysis revealed that step length values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.4 A). For condition SlipRol there was a significant differences in step length of the recovery step between NW, NLoB and LoB trials ($F(2,80) = 148.2$, $p < 0.001$). Post hoc analysis revealed that step length values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.4 B). For condition SlipFoam there was a significant differences in step length between NW, NLoB and LoB trials ($F(2,91) = 142.5$, $p < 0.001$). Post hoc analysis revealed that step length values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.4 C). For slip-perturbation trials of condition SlipTripFoam there were significant differences in step length between NW, NLoB and LoB trials ($F(2,79) = 118.3$, $p < 0.001$). Post hoc analysis revealed that step length values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.4 D). For slip-perturbation trials of condition SlipTripOBFoam there was a significant differences in step length between NW, NLoB and LoB trials ($F(2,78) = 93.05$, $p < 0.001$). Post hoc analysis revealed that step length values were significantly lower in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.4 E).

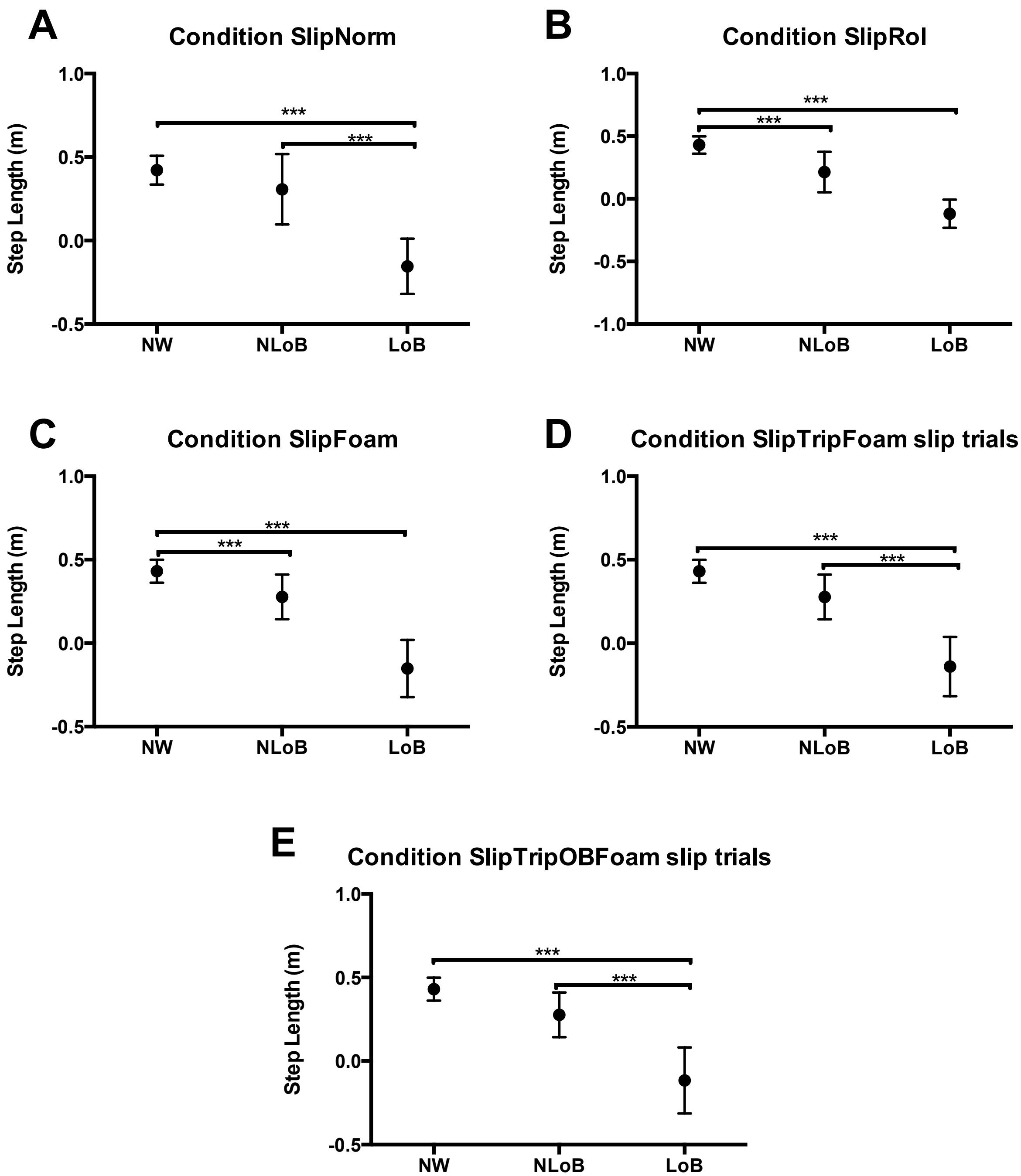

Figure 4.4 shows means and standard deviations (SD) of **step length** at the recovery touch down values for 20 older adults during the natural walking (NW) trials (trials in which no perturbation were induced), during the trials in which slip-perturbations did not induce a loss of balance (NLoB), and during the trials in which the **slip-perturbations** induced a loss of balance (LoB) in conditions SlipNorm, SlipRol, SlipFoam, and for slip-perturbation conditions SlipTripFoam and SlipTripOBFoam. Abbreviations: m, meters; NW, natural walking; NLoB, no loss of balance; LoB, loss of balance. SlipNorm, slip-perturbation on normal surface condition; SlipRol, slip-perturbation on rollers surface condition; SlipFoam, slip-perturbation on foam surface; SlipTripFoam, slip and trip-perturbations on foam surface; SlipTripOBFoam, slip and trip-perturbations with obstacles on foam surface***p<0.001.

For maximum trunk angle after trip-perturbations, there were significant differences between NW, NLoB and LoB trials in TripOB condition ($F(2,83) = 26.47$, $p < 0.001$). Post hoc analysis revealed that maximum trunk angle values were significantly higher in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.5 A). For TripOBFoam condition there were significant differences in maximum trunk angles between NW, NLoB and LoB trials ($F(2,91) = 12.87$, $p < 0.001$). Post hoc analysis revealed that maximum trunk angle values were significantly higher in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.5 B). For trip-perturbation trials in condition SlipTripFoam there were significant differences in maximum trunk angle between NW, NLoB and LoB trials ($F(2,74) = 1.368$, $p = 0.26$). Post hoc analysis revealed that maximum trunk angle values were significantly higher in LoB trials compared to NW ($p<0.001$), however no differences were observed between NLoB and LoB trials ($p = 0.12$) (Figure 4.5 C). And for trip-perturbation trials of condition SlipTripOBFoam there were significant differences in maximum trunk angle between NW, NLoB and LoB trials ($F(2,82) = 12.87$, $p = 0.44$). Post hoc analysis revealed that maximum trunk angle values were significantly higher in LoB trials compared to NW and NLoB trials ($p<0.001$) (Figure 4.5 D).

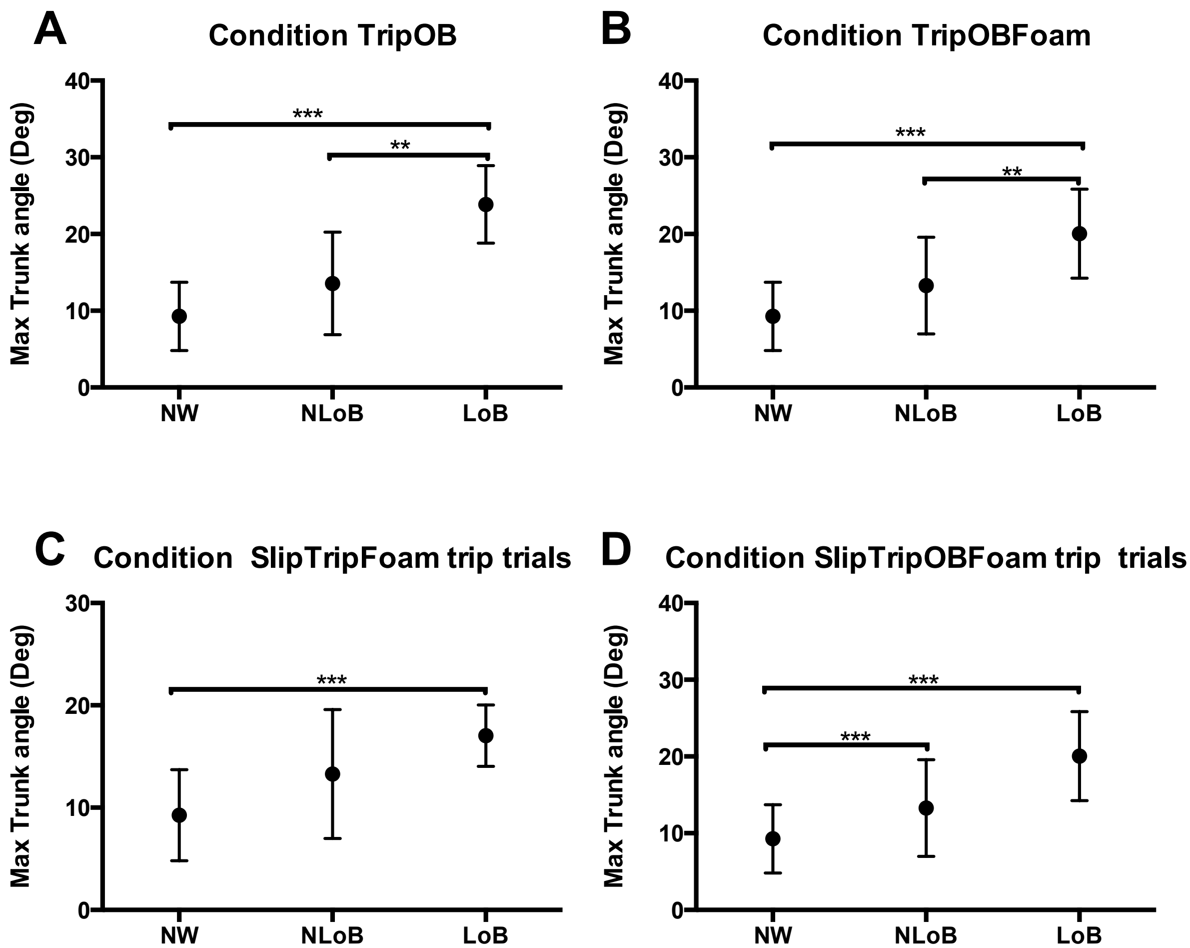

Figure 4.5 shows means and standard deviation (SD) of maximum trunk angle average values for 20 older aduts during natural walking trials (NW) (trials in which no perturbation were induced), during the trials in which **trip-perturbations** did not induce a loss of balance (NLOB), and during the trials in which the **trip-perturbations** induced a loss of balance (LoB) in conditions TripOB and TripOBFoam, and for trip-perturbation trials of conditions SlipTripFoam and SlipTripOBFoam. **Abbreviations:** Deg, degree; NW, natural walking; NLoB, no loss of balance; LoB, loss of balance. TripOB, Trip-perturbations with obstacles; TripOBFoam, Trip-perturbations with obstacles on foam surface; SlipTripFoam, slip and trip-perturbations on foam surface; SlipTripOBFoam, slip and trip-perturbations with obstacles on foam surface. ***p<0.001, ** p<0.01.

4.3.5 Comparison between protocol conditions

Considering all the trials (NLoB and LoB), there was a significant difference in MOS between the training conditions included in the Surefooted protocol in healthy older adults as determined by one-way ANOVA ($F(7,482) = 41.92$, $p < 0.001$). Post hoc analysis revealed that conditions

SlipRol, SlipFoam, and slip-perturbation trials for conditions SlipTripFoam and SlipTripOBFoam were the most unstable training conditions compared to natural walking trials (the trials with no perturbations) ($p<0.001$) (Figure 4.6 A), and that MOS was not significantly different in conditions TripOB, TripOBFoam, and trip-perturbation trials for conditions SlipTripFoam and SlipTripOBFoam compared to natural walking trials (Figure 4.6 B). Similarly, there was a significant difference in the step length at the first recovery step between the training conditions included in the Surefooted protocol as determined by one-way ANOVA ($F (7,484) =29.30$, $p <0.001$). Post hoc analysis revealed that conditions SlipRol, SlipFoam, and slip-perturbation trials for conditions SlipTripFoam and SlipTripOBFoam were the conditions in which participants performed the shortest step length during the first recovery step after perturbations ($p<0.001$) (Figure 4.6 C), and that step length of the first recovery step were not significantly different in conditions TripOB, TripOBFoam, and trip-perturbation trials for conditions SlipTripFoam and SlipTripOBFoam compared to natural walking trials (Figure 4.6 D).

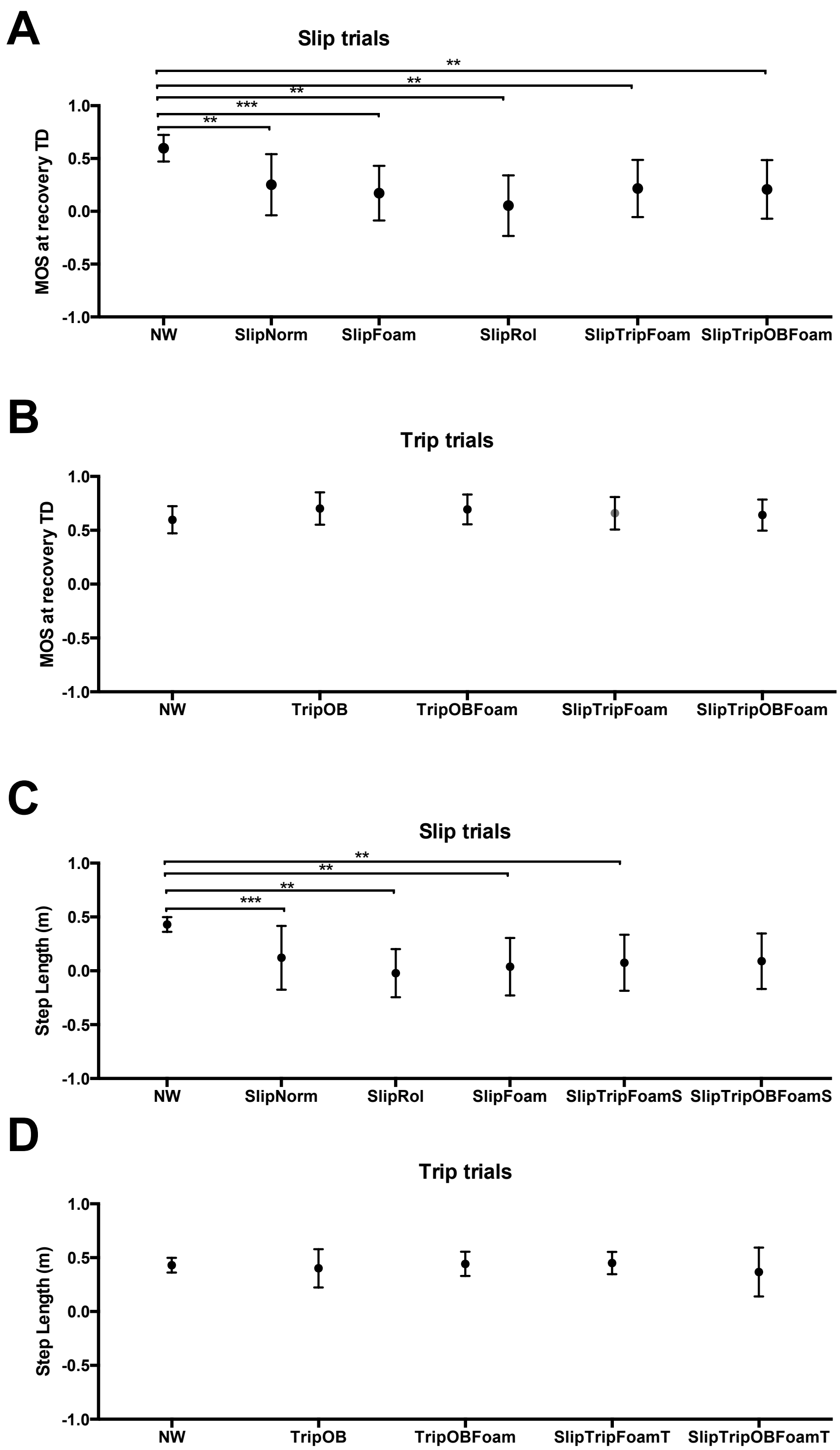

Figure 4.6. Comparisons of means and standard deviations (SD) of MOS in slip (figure 6 A) and trip-perturbation (figure 6 B) training conditions compared to natural walking trials, and comparison of means and standard deviation (SD) of step length at the recovery touch down between training conditions compared to natural walking trials (C: slip-perturbation conditions, D: trip-perturbation conditions). Each condition includes both no loss of balance and loss

of balance trials. Abbreviations: MOS, Margin of Stability; m, meters; NW, natural walking; NLoB, no loss of balance; LoB, loss of balance. SlipNorm, slip-perturbation on normal surface condition; SlipRol, slip-perturbation on rollers surface condition; TripOB, Trip-perturbations with obstacles; SlipFoam, slip-perturbation on foam surface; TripOBFoam, Trip-perturbations with obstacles on foam surface; SlipTripFoam, slip and trip-perturbations on foam surface; SlipTripOBFoam, slip and trip-perturbations with obstacles on foam surface. ***p<0.001, ** p<0.01.

4.3.6 Comparison between heathy older adults and persons with stroke

The percentage of loss of balance in SlipNorm and Slipfoam conditions were 66.6% and 77.7% respectively in PwCS (Table 4.2), which was significantly higher compared to the percentage of loss of balance observed in the group of healthy older adults in the same study conditions (41.25 % in SlipNorm condition and 51.25 in SlipFoam condition). Additionally, for MOS values, the 2x2 ANOVA showed a significant main effects of groups $F(1,111) = 29.31$, $p < 0.01$, a main effect of condition $F(1,111) = 12.97$, $p < 0.01$, and a group by condition interaction $F(1,111) = 5.33$, $p < 0.05$. Post-hoc analysis showed that MOS values were significantly lower in PwCS compared to healthy older adults after slip-like perturbation trials on SlipNorm condition and on SlipFoam condition (Figure 4.7A and Figure 4.7B). For Step length, the 2x2 ANOVA showed a significant main effects of groups $F(1,111) = 4.46$, $p<0.05$, however no effect of condition $F(1,111) = 0.66$, $p > 0.05$, and no group by condition interaction $F(1,111) = 0.78$, $p > 0.05$ was observed. Post-hoc analysis showed that PwCS performed longer backward step compared to healthy older adults after slip-like perturbation trials in both SlipNorm and SlipFoam conditions (Figure 4.8A and Figure 4.8B).

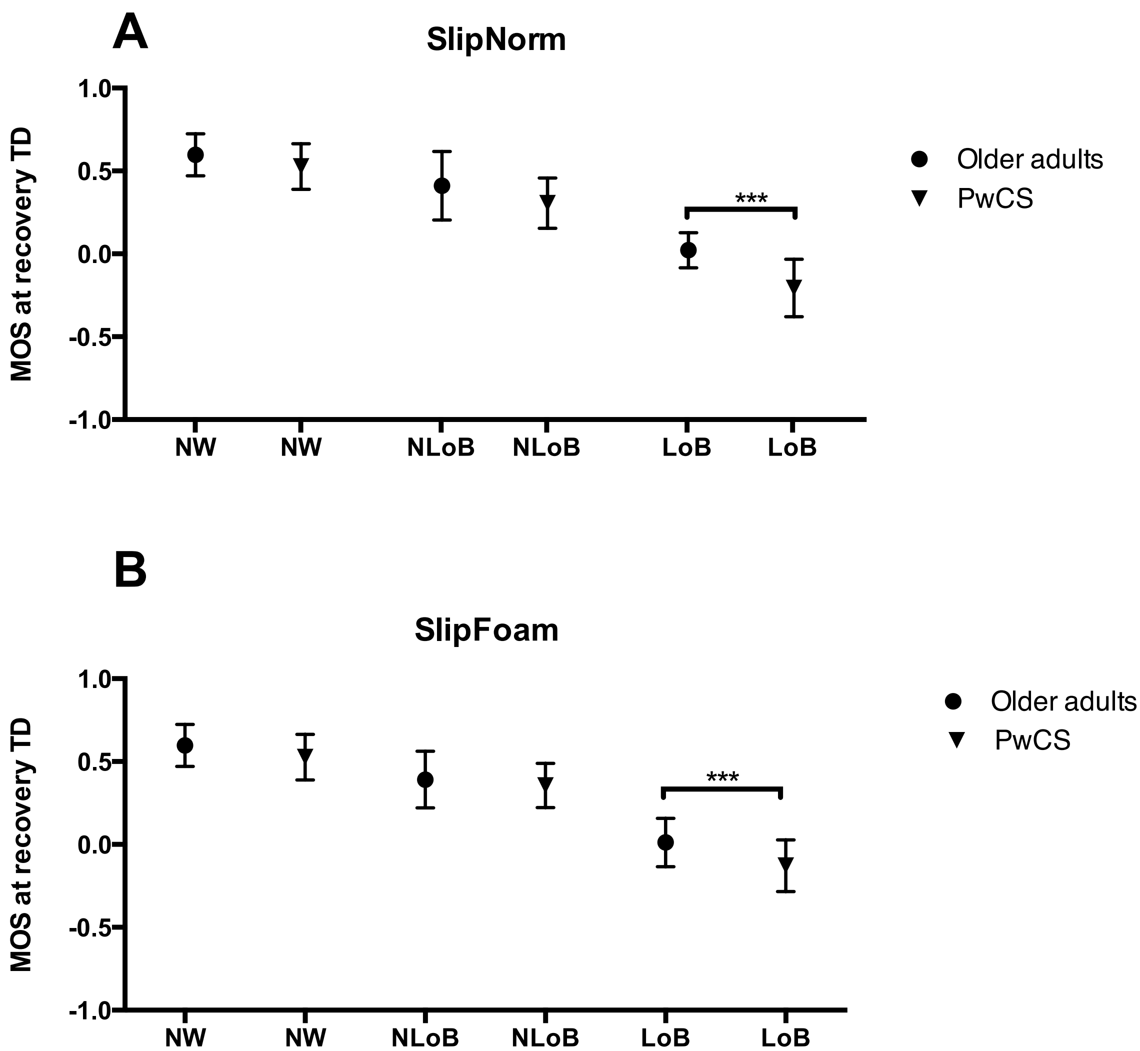

Figure 4.7. Comparisons of means and standard deviations (SD) of MOS between older adults and persons with chronic stroke (PwCS) during SlipNorm condition (Figure 7A) and SlipFoam condition (Figure 7B) for natural walking, no loss of balance and loss of balance trials. Abbreviations: MOS, Margin of Stability; NW, natural walking; NLoB, no loss of balance; LoB, loss of balance. SlipNorm, slip-perturbation on normal surface condition; SlipTripFoam. ***p<0.001.

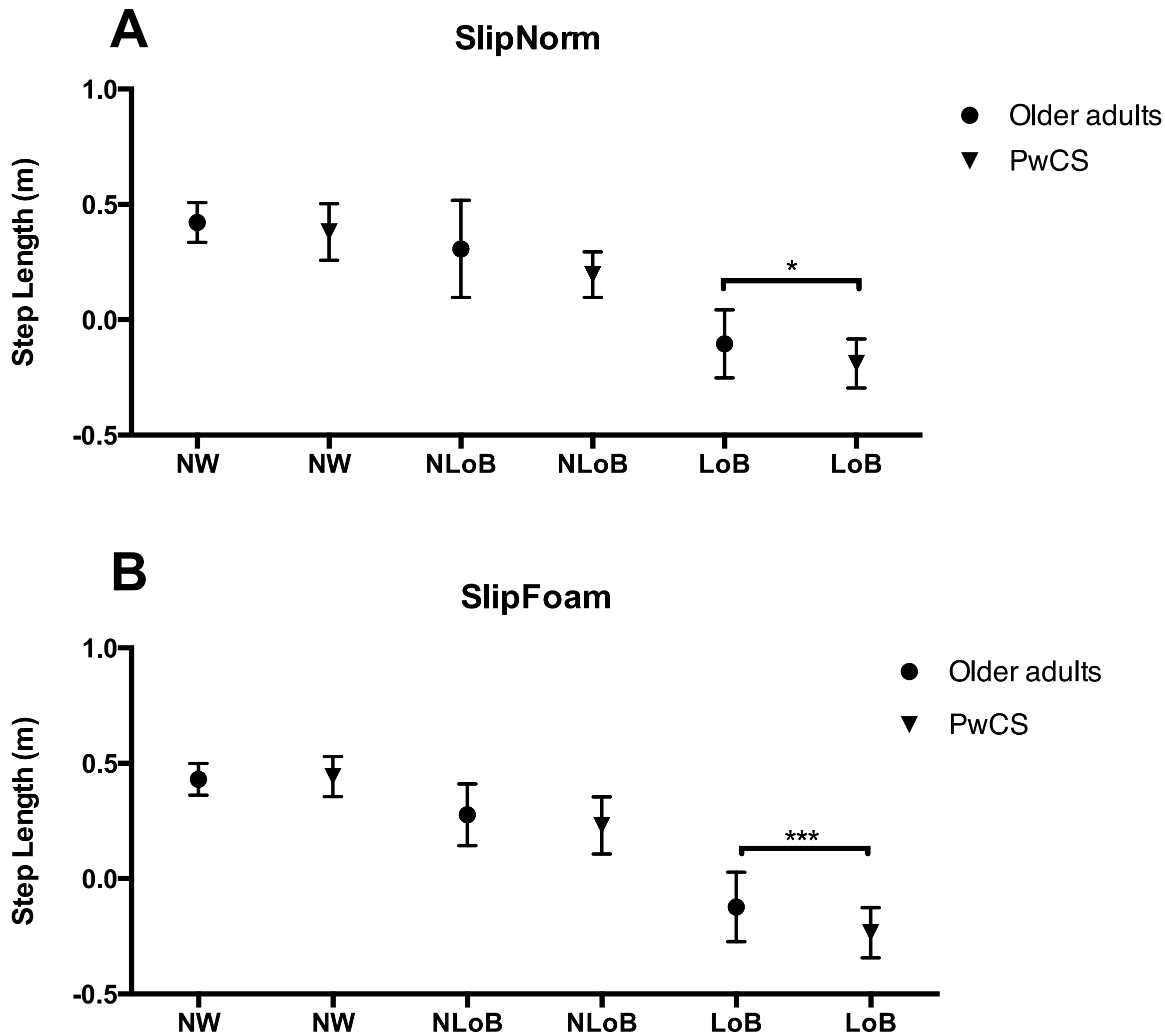

Figure 4.8. Comparisons of means and standard deviations (SD) of Step length of the first recovery step after perturbation between older adults and persons with chronic stroke (PwCS) during SlipNorm condition (Figure 7A) and SlipFoam condition (Figure 7B) for natural walking, no loss of balance and loss of balance trials. Abbreviations: m, meters; NW, natural walking; NLoB, no loss of balance; LoB, loss of balance. SlipNorm, slip-perturbation on normal surface condition; SlipTripFoam. ***p<0.001, * p<0.05.

4.4 Discussion

The primary objective of this study was to examine the feasibility of a novel computer-controlled movable platform to induce slip and trip-perturbations under various sensory conditions in healthy older adults. The second aim of this study was to test the validity of this novel computer-controlled movable platform, comparing behavioral and objective biomechanics parameters in seven different sensory walking conditions, to implement a walking perturbation-based protocol in healthy older adults. A third aim of this study was to compare behavioral and objective biomechanics parameters between healthy older adults and persons with chronic stroke in two slip-like perturbation conditions induced by the Surefooted Trainer. Our findings indicate that the novel computer-controlled movable platform used in this perturbation-based protocol was capable of safely inducing losses of balance in each sensory condition included in this study in healthy older adults. Additionally, we demonstrated that our intervention was acceptable for most participants, practical given our resources, and capable of eliciting positive effects on a limited scale. Similarly, we demonstrated that stability values were lower and the percentages of loss of balance were higher during the slip-perturbation trials in which the somatosensory conditions were more challenging (walking over rollers (SlipRol) and walking over a foam surface (SlipFoam)). Finally, it was also observed that PwCS showed higher incidence of loss of balance and lower stability values compared to healthy older adults during slip-like perturbation induced by the Surefooted Trainer, especially in condition in which somatosensory information was disturbed.

4.4.1 Feasibility

We determined that the perturbation-based protocol implemented in this study using the Surefooted Trainer was acceptable and safe for nearly all of our participants. Only one participant dropped out due to fear of falling caused by the characteristics of the device, arguing that the unpredictability of the perturbation, and the metallic rollers used in condition SlipRol increased his anxiety and fear of falling. One thing that likely helped maintain adherence in our study was that the difficulty of the protocol increased progressively (starting the intervention asking the participants to walk in a condition without any sensory modifications (SlipNorm condition)). Additionally, exercise has been shown to be an effective treatment for fear of falling (Zijlstra et al, 2007), yet the effects of perturbation-based interventions on psychological factors are not well known. Given the task-specific approach implicit in perturbation-based interventions, we suspect that giving subjects experience practicing walking with perturbations in a safe environment is beneficial in building confidence, improving falls self-efficacy, and reducing the fear of falling, which in turn could have contributed to the high acceptance of the protocol among the participants.

The Surefooted Trainer protocol required little space and few staff to administer it. Additionally, in contrast to training protocols in which a therapist has to induce the balance disturbance manually (Mansfield, Wong, Bryce, Knorr, & Patterson, 2015), the perturbations provided by the Surefooted Trainer were more precise and repeatable within and across administrators. This level of control allows for the consistent application and objective analysis of performance-based measures within and across sessions, achieving objectivity levels as good as those observed in treadmill and overground devices. This makes the Surefooted Trainer a good alternative to train reactive balance as good as other moveable platform devices (such as treadmills) while mimicking an overgound surface and adding the possibility to experience perturbations under different sensory conditions.

4.4.2 Discriminative validity

For slip-perturbation protocols (SlipNorm, SlipRol, SlipFoam, SlipTripFoam and SlipTripOBFoam), in the trials in which a loss of balance was induced it was possible to observe significantly lower stability values (MOS and step length) (Figure 4.2 and 4.4), which confirmed the capability of the system to induce losses of balance. On the other hand, for trip-perturbation trials (TripOB, TripOBFoam, SlipTripFoam and SlipTripOBFoam), the MOS values were similar between loss of balance and no loss of balance trials (Figure 4.3), however when we assessed trunk angle during the loss of balance trials we observed that in those trials, the maximum trunk angle was higher compared to the no loss of balance trials which can be assumed as an indicator of instability (Figure 4.5). This allows us to infer that the system was able to induce losses of balance during trip-perturbation trials, however in a lower magnitude compared to the slip-perturbation conditions.

Stability values (MOS and step length) were significantly lower during slip-perturbation trials than baseline. However, this was not the case for trip-perturbations where MOS for baseline and trip-perturbations trials were comparable, showing that trip-perturbation protocols were not as effective or might be less challenging for inducing loss of balance than the slip-perturbation protocols. Similarly, previous studies have shown a significantly greater proportion of falls during backward loss of balance compared to forward loss of balance at the same perturbation intensity in different populations (Hsiao & Robinovitch, 1998; Patel & Bhatt, 2018). Several mechanisms may independently or in combination underlie these directional differences. Grabiner et al have proposed that arresting backward motion of the trunk during a slip is more challenging than forward trunk movement during a trip resulting in higher falls incidence during slips, arguing that differences in base of support and signals arising from visual, proprioceptive, and vestibular sensory systems with perturbation direction may be responsible for these results (Grabiner et al, 2008). Similarly, the impact of a forward-directed perturbation (slip-perturbation) may be stronger because the base of support is smaller for backward compensatory strategies (backward recovery step) compared with compensatory strategies performed in forward directions (such as forward recovery step). Additionally, it has been shown that during slip-perturbations the visual information available regarding the compensatory strategies necessary to maintain balance are lower compared to the visual information available during forward loss of balance (Woollacott, Shumway-Cook & Nashner, 1986), making visual feedback less effective when perturbed backward, possibly creating difficulty in organizing postural reactions to backward falls (Woollacott, Shumway-Cook & Nashner, 1986). All this could explain, in part, the kinematic outcomes observed in our study, and the lower amount of loss of balance observed in the sessions that included trip-perturbation trials in our protocol. However, it might be possible that increasing intensity of the backward/forward platform movement (velocity and/or acceleration), and/or increasing the obstacle height, could generate major levels of instability and increase the difficulty of the protocol proposed in this study, especially for trip-perturbation protocols.

4.4.3 Perturbation-based intervention and sensory integration

A higher percentage of loss of balance trials (Table 4.2), and lower stability values (Figure 4.6) were observed during the protocol conditions in which the walking surface was modified (SlipRol, SlipFoam, SlipTripOBFoam), and in PwCS compared to healthy older adults in SlipNorm and

SlipFoam conditions. In line with these results, it has been well described that more sensory noise results in less reliable sensory information, which can be compensated by an increased use of the information of the other sensory systems (i.e. sensory reweighting) (Pasma et al, 2014). Similarly, evidence has shown that the use of proprioceptive information increases, and the vestibular and visual systems deteriorate more with age compared with the proprioceptive system, resulting in more sensory noise in the vestibular and visual information (Pasma et al, 2014). In our study, the use of rollers in healthy older adults, simulating a slippery surface, and the use of foam either in healthy older adults as well as in PwCS altered the proprioceptive information during walking, adding more difficulty to react to the perturbation triggered by the computer-controlled moveable platform, which could explain the performance observed in our participants in these particular conditions including in our protocol, and the differences observed between healthy older adults and PwCS, especially in SlipFoam condition in which the somatosensory information is disturbed.

It has been also well described that a deterioration of the neuromuscular system to sense the boundary of the base of support in relation to the position of the COM as well as to regain balance after sudden perturbations can be an important risk factor for falls in older adults (Burke, Franca, Meneses, Rodriges Pereira & Marques, 2012; Li et al, 2006; Pasma et al, 2014), and that the control of the COM displacement within the base of support is related more to sensory perception rather than reduced muscle strength (Burke, Franca, Meneses, Rodriges Pereira & Marques, 2012; Moreno Catala, Woitalla & Arampatzis, 2018). In concordance with this evidence, our results showed that MOS values were lower during the conditions in which the somatosensory information was disturbed (SlipRol, SlipFoam, SlipTripFoam and SipTripOBFoam conditions) (Figure 4.6A and 4.6B) and in PwCS compared to healthy older adults (Figure 4.7A and Figure

4.7B). Additionally, step length showed negative values during SlipRol, SlipFoam, and in slip-perturbation trials of SlipTripFoam and SlipTripOBFoam conditions, which was related to the higher percentage of backward loss of balance experienced by the participants in these conditions (Figure 4.6 C). Similarly, step length values of the recovery step were significantly more negative in PwCS compared to healthy older adults in SlipFoam condition (Figure 4.8), which is in line with the higher incidence of loss of balance (in the SlipNorm condition) and lower stability values (in both SlipNorm and SlipFoam conditions) observed in PwCS during the Surefooted Trainer protocol.

4.5 Limitations of the study

We acknowledge certain limitation of this study. First, in this study the average of behavioral and kinetic data of all the perturbation trials for each block are reported, without showing the trial to trial changes. However, due to unpredictability of each perturbation trials and the inclusion of walking trials between perturbation trials, trial to trials adaptations to external-induced perturbations were minimal. In this context more studies are needed to see if trial to trial changes can be observed within one-session or over multisession training protocols. Second, a limitation of most moveable-platform perturbation systems that for the trip-perturbations, it is not possible to replicate the sensory and motor conditions that arise when the swing phase of gait is obstructed by an external obstacle. However, the Surefooted Trainer's backward platform movement does create an overall pattern of whole-body motion that is similar to what occurs following an actual trip (COM displaced forward relative to the anterior most foot). In addition to the backward surface displacement the addition of obstacles (via the tethered rope) that make the trip experience more reliable.

4.6 Conclusions

In summary, we have shown that a fall-recovery protocol using a novel computer-controlled moveable platform device is an acceptable, practical, and valid therapeutic tool to develop PBT for healthy older adults. Our initial results suggest that this new intervention device could induce balance loss, which was correlated with objective biomechanical stability values for both slip and trip-perturbations. Additionally, the highest percentage of loss of balance and the lowest stability values were observed in the conditions in which slip-perturbation trials were induced in combination with proprioceptive disturbances (SlipRol and SlipFoam conditions), and in PwCS compared to healthy older adults. Future studies should be conducted in order to extend this work, examining if fall-resisting skills can be acquired with repeated exposure (perturbation-based training) under all of these conditions representing higher levels of unpredictability and diverse sensory conditions and opposing perturbation types (slips and trips). Additionally, future researches should test the preliminary findings observed in this study in a randomized controlled trial and with a larger cohort with more impairments or in persons with other neurological disorders, and evaluating its effects on balance self-confidence, walking activity, and subsequent falls in the free-living environment.

Chapter 5

Application of neuromuscular electrical stimulation on the support limb during reactive balance control in persons with stroke

5.1 Introduction

Falling is one of the most common complications that occur among persons with stroke (PwS) (Davenport et al. 1996), with this population sustaining more than a two-fold increase in fall risk when compared with healthy age-matched individuals (Jørgensen et. 2002). Reactive components of balance control are critical to maintaining stability following a postural disturbance (Maki and McIlroy 1997). Thus, response to change in body support, involving rapid compensatory stepping and/or grasping reactions that increase the size of the base of support are essential to prevent falling (McIlroy and Maki 1993). However, successful change-in-support responses depend upon the high speed of execution combined with accurate limb placement (McIlroy and Maki 1993), motor strategies (that are often impaired in PwS, who tend to exhibit multistep responses), delayed time to initiate and/or complete stepping and the possibility of complete inability to initiate stepping with the paretic limb (Innes et al. 2014; Mansfield et al. 2011; Mansfield et al. 2012; Lakhani et al. 2014). These characteristics create a tremendous demand on PwS, in particular those with stroke-related hemiparesis, making the control of change-in-support responses one of the most challenging sensorimotor behavior among this population (Harburn et al. 1995; Jensen et al. 2001; Mansfield et al. 2013; Mansfield et al. 2015; Lakhani et al. 2010).

Following an unexpected balance perturbation, postural responses triggered by external disturbances are initiated to maintain upright stability, with the central nervous system (CNS) utilizing and integrating the available sensory and environmental information to select an appropriate response strategy (Marigold and Eng 2006). Along this line, balance perturbations evoke an early postural muscle response with onset latencies as early as 100 ms that are predominantly mediated by spinal reflexes (Marigold and Eng 2004). Subsequently, it is postulated that a large group of muscles are quickly activated via the long-loop brain stem responses (a triggered postural synergy) to generate forces that modulate an appropriate motor strategy (in-place versus stepping) to counteract the destabilizing forces imposed by the postural perturbation (Kirker et al 2000; Marigold and Eng 2004; Marigold and 2006). However, due to sensorimotor impairments in PwS, these early components of the muscle response after a balance disturbance as well as the ability to generate the triggered postural synergies are delayed and smaller in amplitude compared to healthy individuals (Kirker et al 2000; Marigold and 2006). Additionally, studies have shown that stroke-related deficits in sensorimotor responses are more pronounced in individuals who have fallen in response to imposed posterior perturbations when compared with those who successfully restored balance (Marigold and Eng 2006). In concordance with all these evidence, several studies have described that PwS have delayed paretic limb muscle onset latencies following perturbations while standing on a moveable platform compared to their non-paretic limb and compared to healthy older adults (Berger et al. 1988; Dietz et al. 1984; Di Fabio et al. 1988; Marigold and Eng 2004). Considering that usually compensatory steps are more frequently initiated with the non-paretic limb than with the paretic limb, the function of supporting the whole body during reactive stepping from the paretic limb might cause stability problems in PwS due to the muscle activity delay after balance disturbance and thus overall affected reactive response (Mansfield et al. 2012; Lakhani et al. 2011).

It has been well described that knee extension of the support limb is one of the most important kinematic variables that contributes to stability and the prevention of a limb collapse after an external balance disturbance (Pijnappels et al. 2005; Wang et al. 2019). Along these lines, Wang et al. (2019) examined the most frequent biomechanics causes of fall in older adults during external induced walking perturbations and found that limb collapse was the major cause of falls as well as the cause of repeated falls among older adults. These findings are in concordance with the long-held notion of age-related deterioration in muscle strength and force production rate (Burr and Bone 1997; Moreland et al. 2004). Similarly, it has been shown that hip height value, a kinematic indicator of limb collapse, after a slip-like perturbation was correlated to vertical ground reaction force, which in turn correlates with the net extensor moment to maintain upright stance with the support limb, therefore allowing an efficient stepping response with the contralateral limb (Patel and Bhatt 2015; Salot et al. 2016). Further, it has also been shown that PwS present higher incidence of limb collapse after a slip-like perturbations, which increases with the intensity of the disturbance and thus affects the stepping response of the contralateral limb and stability values during the reactive response (Salot et al. 2016). All of these variables can contribute to the higher levels of falls incidence observed in the PwS population compared to healthy older adults (Patel and Bhatt 2015; Pijnappels et al. 2005; Salot et al. 2016).

In line with the evidence that has described the relevance of the change in post-perturbation vertical limb support to prevent falls, studies have shown that biarticular thigh muscles (hamstring and rectus femoris) play an important role on maintaining an extension torque, thus helping the support limb to maintain stability during the reactive response after a loss of balance (Schumacher et al 2019; Tang et. 1998). Along this line, Schumacher et al. (2019) reported that rectus femoris (RF) showed the strongest electromyographic response of the support limb after a stance balance perturbation, confirming the relevance of this lower limb biarticular muscle on maintaining an extension torque and restoring balance control. Although all these findings hint at a causal relationship between defective early and late components of the recovery response, motor impairment and poorer postural stability after a balance disturbance, the strength of this relationship in PwS is unknown.

In recent years, neuromuscular electrical stimulation (NMES) techniques, defined as an intervention that uses electrical stimulation to produce contraction of paretic muscles (Knuston et al. 2015), has been used to activate muscles during functional tasks with the goal of improving motor activity performance in PwS (Everaert et al. 2010; Knuston et al. 2015). NMES can be used to stimulate the neuromuscular activity of the paretic limbs after stroke because normal electrical excitability often remains in lower motor neurons and their innervated muscles (Everaert et al. 2010). Thus, several studies have shown that NEMS reduces disability by improving the recovery of volitional movement (therapeutic effect) or by assisting and replacing lost volitional movement (neuroprosthetic effect) (Gervasoni et al. 2017; Knuston et al. 2015; Santos et al. 2006). A few meta-analysis (Kottink et al. 2004; Pereira et al. 2012; Robbins et al. 2006) and several pilot studies (Bogatai et al. 1995; Everaert et al. 2010; Gervasoni et al. 2017; Kimberley et al. 2004; Sheffler et al. 2013) have demonstrated improvements on gait parameters and lower limb functions during voluntary balance tasks with the use of NMES in PwS. However, the efficacy of the application of NMES techniques in lower limb muscles of PwS during reactive balance responses has not been explored before.

Falls generated in a laboratory setting can be induced in such a way that every individual is exposed to the same destabilizing force. Consequently, the kinematic mechanisms associated with the reactive balance strategies performed by the participants can be quantified. In this study, we aimed to examine whether the application of neuromuscular electrical stimulation applied to the rectus femoris muscle of the support limb, triggered in synchrony with a large magnitude backward and forward externally induced stance perturbation, improves stability values and reactive motor strategies in persons with chronic stroke. We hypothesized that the application of NMES in the rectus femoris muscle of the support limb will contribute to prevent the limb collapse after a stance treadmill perturbation, improve the reactive stepping response as well as stability control and enhance the overall behavioral outcome to the support-surface perturbation in persons with chronic stroke.

5.2 Methods

5.2.1 Participants

Ten community dwelling persons with chronic stroke (PwCS) (> 6 months post-stroke) (2 females and 8 males, aged 62.2±4.6) participated in the study. Participants were included if they were able to walk independently with or without an assistive device. On the other hand, participants with cognitive deficits (score of < 26 on Montreal Cognitive Assessment Scale), speech deficits (aphasia score of > 71/100 on Mississippi Aphasia Screening Test), or presence of any other neurological, musculoskeletal, or cardiovascular conditions were excluded from the study. Additionally, the preferred stepping leg after a slip- and trip-like perturbation was tested during the familiarization trials. Participants who preferred to use the paretic limb as stepping leg were also excluded of the study. The number of years since stroke, and participants' usage of ankle foot orthoses (AFO) for community ambulation were documented. Additionally, baseline functional status assessments, including severity of impairment (Chedoke-McMaster Stroke Assessment), and balance testing (Berg Balance Scale, and Timed Up and Go) were performed. All participant has a normal or corrected to normal vision. Demographic details and baseline clinical assessments are presented in Table 5.1. A written informed consent was obtained from all participants before they were enrolled in the study. The study was approved by the Institutional Review Board of the University of Illinois at Chicago.

Variables	Baseline
Age (years)	62.2±4.6
Weight (Kg.)	77.9±10.05
Hight (cms)	174.43±5.2
MOCA test	26.7±1.8
TUG (s)	10.9±5.1
BBS	51.6±3.6
Blood pressure	128±14/93±9.4
Time since stroke (months)	48.6±33.6
Motor Impairment	
CMSA (Leg)	5.3±2.2
CSMA (foot)	4.9±2.7
NASA-TLX after study protocol	
Mental demand	3.4±6.7
Physical Demand	13.4±24.6
Temporal Demand	5.1±13.6
Performance	67.4±33.8
Effort	55.7±16.4
Frustration Level	4.7±4.8
Global Score	24,95

Table 5.1. Participants' demographic data and baseline cognitive and motor assessments. In addition, table 5.1 shows mean and standard deviations (SD) of NASA-TLX results.

5.2.2 Experimental Protocol

Before starting the experimental protocol, the amplitude and frequency of the current delivered by the NMES device was tested in each participant with the aim of checking if it was comfortable and did not produce any type of pain. Additionally, during this testing process, the amplitude in which the current was going to be applied was adjusted and determined for each participant. NMES parameters for each participant can be found in Table 5.2.

Participant	Amplitude of NMES	Paretic side
1	35 mA	Right
2	40 mA	Right
3	40 mA	Left
4	38 mA	Left
5	44 mA	Right
6	43 mA	Right
7	42 mA	Left
8	42 mA	Right
9	45 mA	Right
10	37 mA	Left

Table 5.2. Table 5.2 shows the amplitude of the electrical stimulation used for each participant. Additionally, it is informed the paretic side of the 10 participants included in the study.

The experimental protocol consisted of experiencing 12 stance treadmill perturbations, 6 slip-like perturbation and 6 trip-like perturbation trials. For each perturbation condition (slip and trip-like perturbations), 3 perturbation trials were delivered synchronized with NEMS applied to the RF of the paretic limb and 3 perturbation trials were triggered without NEMS (Fig. 5.1). The ActiveStep (Simbex) motorized treadmill was used to deliver stance slip and trip-like perturbations in this study. A safety harness was attached to the participant to prevent them from touching the treadmill belt in case of fall. All participants were informed that during the experiment they were going to experience a forward (slip-like perturbation) or backward (trip-like perturbation) treadmill belt displacement without any prior announcement. Additionally, they were also informed that for some of the perturbation trials they were going to feel a current applied by NEMS device in the anterior part of the thigh area of the paretic limb at the same moment of the perturbation (Fig. 5.2).

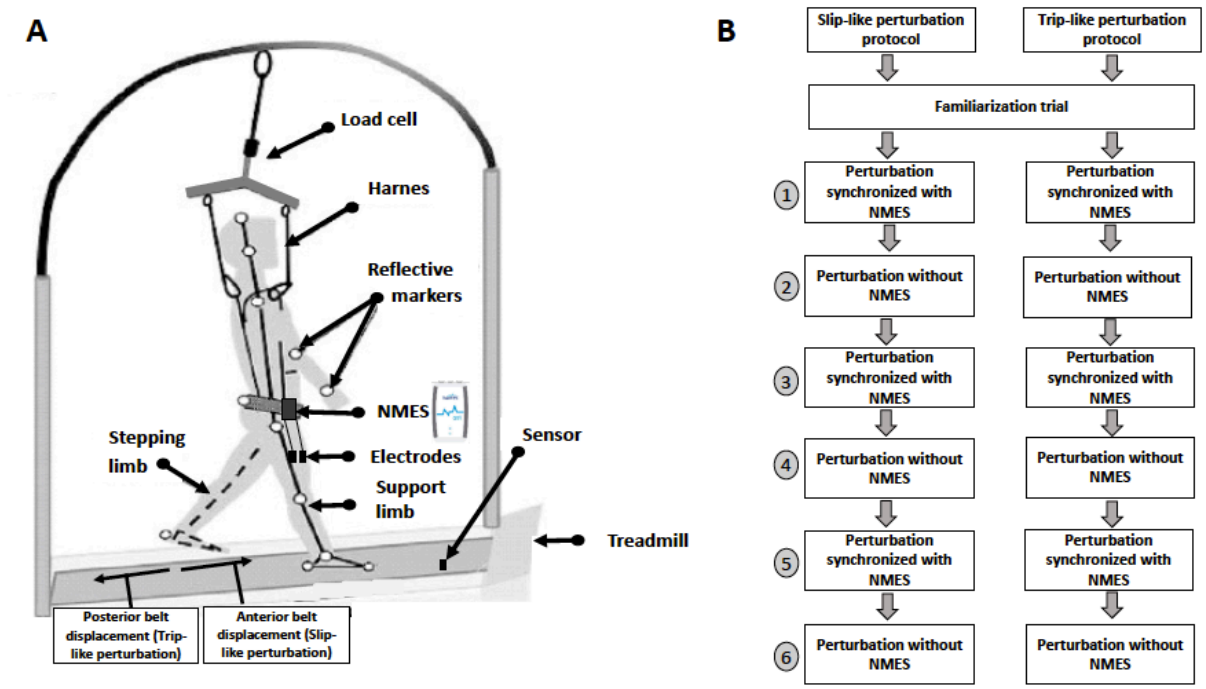

Figure 5.1. Experimental setup and conceptual framework of the study design.

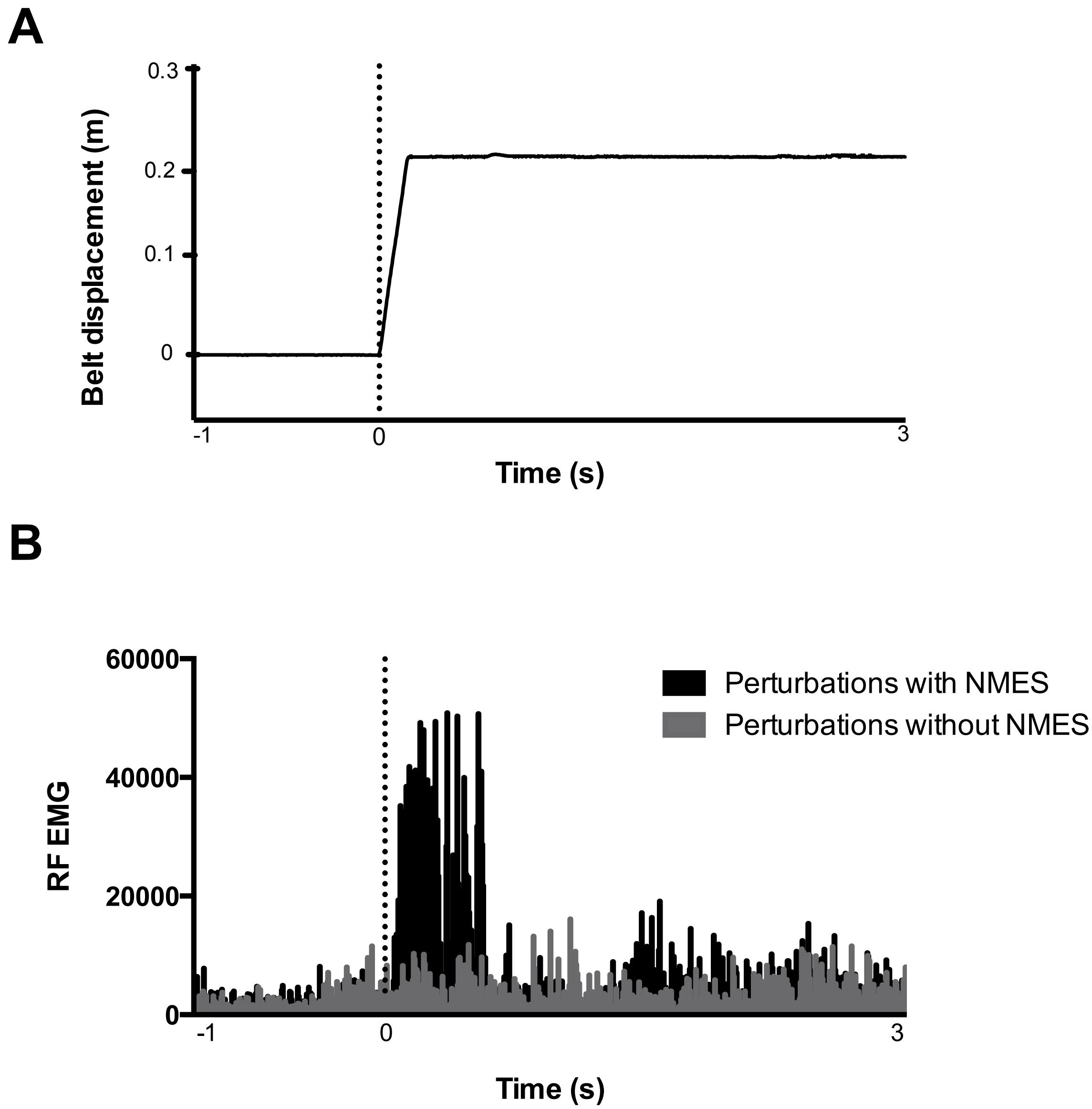

Figure 5.2. A) Belt displacement during a slip-like perturbation trial based on the belt marker displacement. Figure depict the nature of the slip perturbation. in which the time 0 and the vertical dotted line represent the perturbation onset. **B)** Representation of the electrical signal recorded from the electrodes placed on the paretic RF of one participant during a slip-like perturbation trial with and without NMES. For both figures, the time 0 and the dotted line represent the moment of the perturbation onset. Abbreviations: m, meters; s, seconds; RF, rectus femoris; EMG, electromyography; NMES, neuromuscular electrical stimulation.

All participants were subjected to familiarization of slip and trip-like perturbation trials at a lower intensity (belt acceleration of 12 m/s^2 for slip-like perturbations (Intensity II) and higher intensity (16.8 m/s$^{2)}$ for trip-like perturbations (Intensity III)) before starting the experimental protocol in order to minimize fear, limit startle response (Dijkstra et al. 2015) and acquaint to the nature of the treadmill perturbations. The timing of the perturbations was not fixed, and perturbations occurred anytime between 5-20 seconds. All participants were asked to stand in alignment with a starting line marked on the treadmill to ensure the same starting position across all the participants.

Following the familiarization trials participants were exposed to the first slip-like perturbation trial (belt acceleration of 16.8 m/s^2 (Intensity III)) synchronized with NEMS applied on RF, the second slip-like perturbation trial was delivered without NEMS, the third slip-like perturbation trial was delivered, again, synchronized with NEMS, the fourth slip-like perturbation trial was delivered without NEMS, and finally the fifth and sixth slip-like perturbations trials were delivered with and without NEMS respectively.

After the slip-like perturbation protocol, another trip-like perturbation familiarization trial was experienced by the participants. After familiarization, participants were exposed to the first trip-like perturbation trial (belt acceleration of 19.24 m/s^2 (Intensity IV)) synchronized with NEMS applied on rectus femoris. Thus, the second, fourth and sixth trip-like perturbation trials were delivered without NEMS, and the first, third, and fifth trip-like perturbation trials were delivered synchronized with NEMS. The distribution of the trials was selected in order to avoid that the adaptation to externally induced treadmill perturbations differentially affect any of the experimental conditions (NMES vs. No NMES conditions). Additionally, both for the slip protocol as well as for the trip protocol, the first perturbation trail was always synchronized with NMES so that, if there was any adaptation component to the treadmill perturbations, it would affect our independent variable (NMES) to a lesser extent.

5.2.3 Neuromuscular electrical stimulation

The specific NEMS device used in this study was a multi-channel system that, comprises a stimulation cuff with two electrodes affixed on the RF area, a control unit, and a sensor sensitive to acceleration changes placed on the treadmill belt to trigger the electrical stimulation at the exact moment of the perturbation onset. The stimulation unit initially was configured by a researcher, who used a handheld wireless computer interface. Stimulation parameters (amplitude 30-45 mA, duration 450 ms, frequency 20-45 pps) were individualized to achieve functional, comfortable, and timely muscle contraction (Table 5.2) (Sabut et al. 2010).

5.2.4 Data collection

An eight-camera 3D motion capture system recording at 120 Hz (Motion Analysis, Santa Rosa, CA) was used to collect full body kinematics. A total of 30 markers from the Helen Hayes marker set were used, with 29 markers on specific bony landmarks on the participant and one on the belt to identify perturbation onset. Data from reflective markers were subjected to low pass filtering using a fourth order Butterwirth filter. The three-dimensional marker position information obtained from the 29 body markers was used to compute the COM position (Davis et al. 1991). A load cell, synchronized with the motion capture system and connected in series with the harness, measured the amount of body weight exerted on the harness during each trial. All kinematic variables were computed using custom written algorithms in MATLAB version 2014b (The MathWorks Inc, Nactick, MA).

5.2.5 Outcome measures

5.2.5.1 Behavioral outcomes

5.2.5.1.1 Falls. Perturbation outcomes were identified as a fall or as a recovery depending on the weight borne by the harness. A fall was determined if the load cell detected more than 30% of the participant's body weight after the perturbation onset (Yang and Pai 2011), or if the participant was assisted by researchers to maintain the standing position after the perturbation (Patel and Bhatt 2018). During the analysis process, the behavioral outcomes were verified by visual inspection of video recording.

5.2.5.1.2 Number of compensatory steps. The number of compensatory steps executed from the onset of the perturbation to the recovery of balance were also recorded based on the step liftoff and touchdown (TD) events (Salot et al 2016).

5.2.5.2 Kinematic outcome measures

5.2.5.2.1 Margin of stability. The margin of stability (MOS) is defined as the distance between a velocity adjusted position of the COM and the edge of an individual´s base of support (BOS) at any given instant in time. It has been described that MOS is directly related to the impulse required to cause instability (Hak et al. 2013; Hop et al 2008). This variable was analyzed at the touch down (TD) before the perturbation and at the liftoff (LO) after the perturbation. Liftoff and touchdown times were determined from the *Z* co-ordinate of the heel and fifth metatarsal markers. Liftoff was identified when the *Z*-trajectory of the stepping foot (heel or metatarsal marker making last contact with the treadmill) exceeded more than two standard deviations from the mean baseline value before the compensatory leg liftoff. The touchdown time was identified as the instant of initial contact of the foot (heel or metatarsal marker) with the treadmill when the *Z*-trajectory of foot marker reached the baseline (i.e., position during quiet stance prior to liftoff of the compensatory step). The liftoff and touchdown times were calculated using a custom program and were manually verified.

MOS was calculated using the equation below, and then normalized by BOS length:

$$MOS = COM + COMv/\sqrt{(g/l)} - BOS_{max}$$

Here COM indicates the position of COM, which was estimated by the sacrum marker, COMv indicates the velocity of COM in anterior-posterior direction, “l” indicates the leg length, and BOS_{max} indicates the edge of the base of support. The BOS length was calculated as foot length in single stance phase, and the distance between toe of the leading foot and heel of the trailing foot in double stance phase.

5.2.5.2.2 Minimum hip height value of the support limb. The minimum hip height value was recorded as the minimum distance from the floor of the midpoint of the hip after perturbation onset (Z_{hip}). The midpoint of the hip was determined from bilateral anterior superior iliac spine reflective markers, and the Z_{hip} was normalized by the individual’s body height.

5.2.5.2.3 Step Length. Recovery step length was measured as the heel-to-heel distance (in meters) between the foot of the supporting limb and the recovery foot at compensatory step TD.

5.2.5.2.4 Step initiation time. The step initiation time was defined as the time taken to liftoff of the stepping limb heel after perturbation

5.2.5.2.4 Step execution time. The step execution time was defined as the time elapsed between LO and TD of the stepping limb.

5.2.6 Analysis

A total of 120 perturbation trials were analyzed in this study, composed of 60 slip and 60 trip-like perturbation trials. From the 60 slip-like perturbation trials, 30 were delivered synchronized with NMES applied to the RF of the paretic limb, and 30 were delivered without NMES. Same amount of perturbation trials with and without NMES were experienced by the participants during the trip protocol.

The percentage of falls, the means of compensatory steps and all kinematic outcome measures were compared between the two conditions studied in the current protocol (reactive balance strategies with NMES applied to the RF and reactive balance strategies without NMES). If the values were normally distributed on the basis of a Kolmogorov-Smirnov test, a paired *t*-test was applied; otherwise non-parametric methods, namely a sign test and a Wilcoxon sign-rank-test were used. All confidence intervals were calculated with a probability of 95%.

To verify the magnitude of the changes after the intervention, the effect size (ES) was calculated based on Cohen's *d*. Effect size is classified as small (d = 0.0–0.20), medium (d = 0.30–0.50), and large (d = 0.50–0.80). The level of statistical significance was set at $p \leq 0.05$. Data were analyzed using the SPSS package 22.0 (SPSS Inc., Chicago, IL, USA).

5.3 Results

All of the participants recruited for this study (2 females and 8 males) completed the experimental protocol successfully. In addition, every participant performed the recovery stepping with the non-paretic limb using the paretic limb as the support limb, which was tested during the familiarization trials and maintained across all the study protocol. Thus, NMES was always applied to the RF of the support limb. Additionally, no serious and non-serious adverse events were reported by the participants among the study protocol, and the electrical stimulation provided by the NMES device was well tolerated by all of the participants. Details about the parameters of the NMES for each participant are presented in Table 5.2.

5.3.1 Behavioral outcome measures

Participants showed a significantly higher percentage of falls when they experienced slip-like perturbations without NMES (43.3 %) compared to the experimental conditions in which slip perturbations were synchronized with NMES (23.3 %) ($p<0.05$). Similarly, for trip-like perturbations, the percentage of falls was higher during the trials in which the perturbation was experienced without NMES (40 %) compared to the trials in which the trip perturbations were synchronized with NMES (20%) ($p< 0.05$) (Fig. 5.3 A and Fig. 5.3 B). However, no differences were observed in the number of recovery steps after perturbations between NMES and no NMES conditions either for slip or trip-like protocol ($p> 0.05$) (Fig. 5.3 C and Fig. 5.3 D).

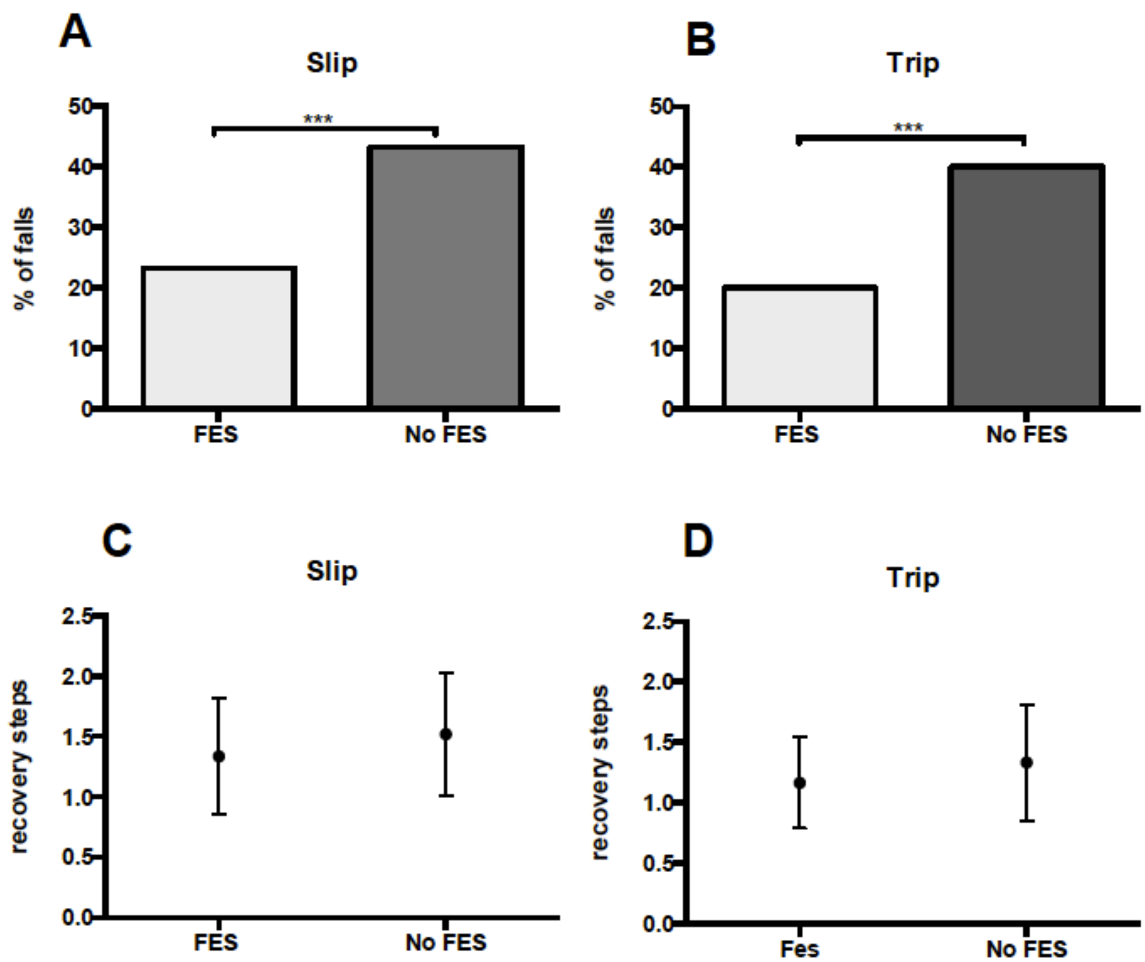

Figure 5.3 shows the results of behavioral outcome measures. Figure 3 A shows the percentage of falls experienced by the participants in the trials in which slip-like perturbations were synchronized with NMES compared to the trials in which slip-like perturbations were triggered without NMES. Figure 3 B shows the percentage of falls experienced by the participants in the trials in which trip-like perturbations were synchronized with NMES compared to the trials in which trip-like perturbations were triggered without NMES. Figures 3 C and 3 D shows the means and standard deviations (SD) of the number of recovery steps performed by the participants after slip and trip-like perturbations triggered with and without NMES respectively. ***$p<0.001$.

5.3.2 Kinematic outcome measures

During slip-like perturbation trials, MOS values at liftoff after the perturbation onset were significantly higher when the perturbation was synchronized with NMES applied to the RF of the paretic limb compared to the perturbation trials in which perturbations were not delivered with NMES ($p< 0.05$) (Fig. 5.4 A). On the other hand, no differences were observed in MOS at liftoff during trip-like perturbation protocol between the trials in which perturbations were synchronized with NMES applied to the RF of the paretic limb compared to the perturbation trials in which perturbations were not delivered with NMES ($p < 0.05$) (Fig. 5.4 B). Similarly, during slip-like perturbation trials, MOS values before the first TD following perturbation onset were significantly higher (more positives) when the perturbation was synchronized with NMES applied to the RF of the paretic limb compared to the perturbation trials in which perturbations were not delivered with NMES ($p < 0.05$) (Fig. 5.4 C). However, during trip-like perturbation trials, MOS values before the first TD after perturbation onset were significantly lower (near to zero) when the perturbation trials were synchronized with NMES applied to the RF of the paretic limb compared to the perturbation trials in which perturbations were not delivered with NMES ($p < 0.05$) (Fig. 5.4 D).

Regarding the kinematic variables related to limb collapse, for slip and trip-like perturbation trials it was observed that the minimum hip height values of the support limb before the first TD after the perturbation onset were significantly higher in the trials in which perturbation trials were synchronized with NMES applied to the RF of the paretic limb compared to the perturbation trials in which perturbations were not delivered with NMES ($p < 0.05$) (Fig. 5.4 E and 5.4 F).

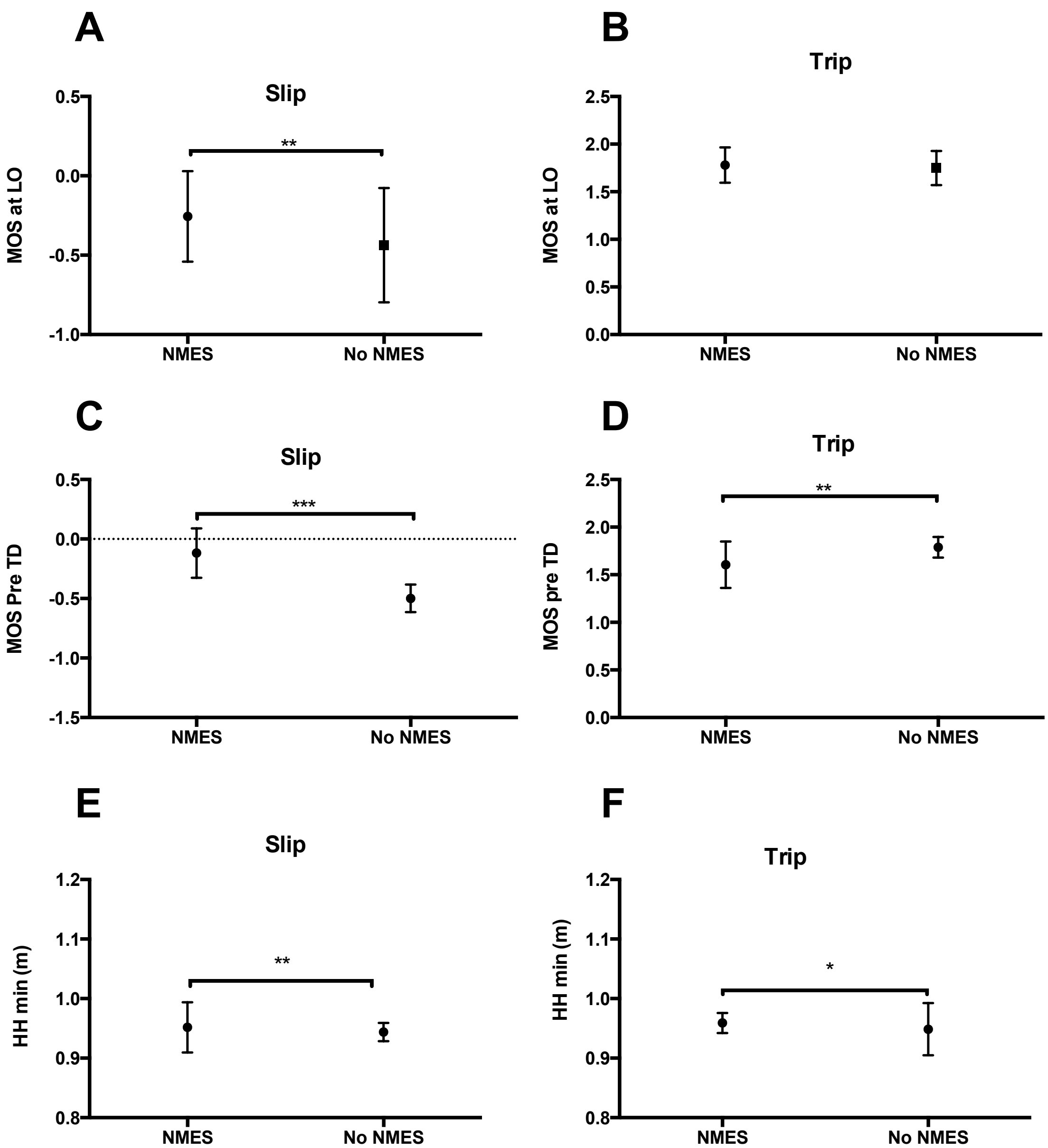

Figure 5.4. Figure 5.4 A shows means and standard deviations (SD) of Margin of Stability (MOS) at liftoff after the perturbation onset in the trials in which slip-like perturbations were synchronized with NMES compared to the trials in which slip-like perturbations were triggered without NMES. Figure 5.4 B shows means and standard deviations (SD) of Margin of Stability (MOS) at liftoff after the perturbation onset in the trials in which trip-like perturbations were synchronized with NMES and in the trials in which trip-like perturbations were triggered without NMES. Figure 5.4 C shows means and standard deviations (SD) of Margin of Stability (MOS) after the perturbation onset and before the touchdown (TD) of the first recovery step in the trials in which slip-like perturbations were synchronized with NMES compared to the trials in which slip-like perturbations were triggered without NMES. Figure 5.4 D shows means and standard deviations (SD) of Margin of Stability (MOS) after the perturbation onset and before the

touchdown (TD) of the first recovery step in the trials in which trip-like perturbations were synchronized with NMES and in the trials in which trip-like perturbations were triggered without NMES. Figures 5.4E and 5.4 F shows the means and standard deviations (SD) of the minimum values of the distance between the floor and the hip (hip height) after slip-like perturbations synchronized with NMES and without NMES (Figure 5.4 A), and after trip-like perturbations synchronized with NMES and without NMES (Figure 5.4 B). * $p<0.05$, ** $p<0.01$, ***$p<0.001$.

Step initiation time of the stepping leg (non-paretic limb) was significantly lower in slip perturbation trials in which the perturbations were synchronized with NMES applied to the RF of the paretic limb ($p< 0.05$) (Fig. 5.5 A). On the other hand, no differences were observed in step initiation times for trip-like perturbation trials (Fig. 5.5 B). Regarding the step execution time of the first recovery step, no differences were observed between the trials in which perturbations were synchronized with NMES and without NMES condition either for slip and trip-like perturbation protocols ($p< 0.05$) (Fig 5.5 C and 5.5 D) Similarly, no differences were observed in step length of the recovery step between the trials in which perturbations were synchronized with NMES and without NMES condition either for slip and trip-like perturbation protocols ($p< 0.05$) (Fig. 5.5 E and Fig. 5.5 F).

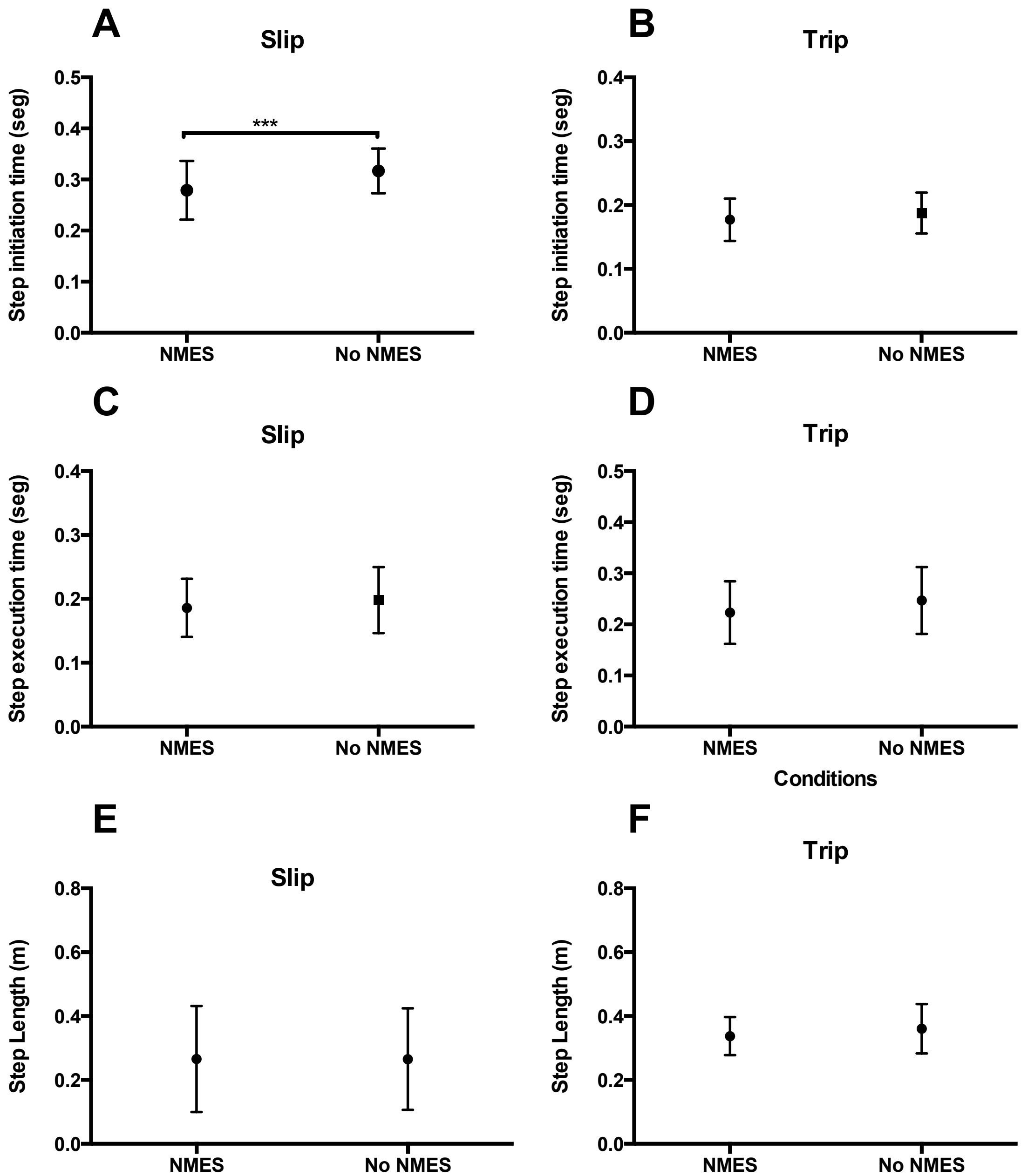

Figure 5.5 shows means and standard deviation (SD) of step initiation time (stepping limb) after slip- and trip-like perturbations synchronized with NMES and after slip- and trip-like perturbations that were triggered without NMES (Figures A and B). Figures 5 C and 5 D shows the step execution time of the first recovery step after slip- and trip like perturbation trials respectively. Figures 5 E and 5 F shows the means and standard deviations (SD) of the step length of the recovery step performed by the participants after slip and trip-like perturbations triggered with and without NMES respectively. ***$p<0.001$.

5.4 Discussion

The aim of the present study was to investigate the effect of the application of NMES to the RF muscle of the paretic limb during externally induced stance slip and trip-like perturbations on reactive balance control in PwCS. Consistent with our hypothesis, the application of NMES on the knee extensor muscles of the paretic limb reduces the incidence of falls and improves stability values as well as kinematic parameters associated with limb collapse after slip and trip-like perturbations in PwCS.

It has been well described that upper motoneuron lesions, such as stroke, affect the neuronal circuitry involved in the generation and organization of postural responses following balance-threatening events, which contributes to the high incidence of falls observed in PwS (Marigold and Eng 2006). Specially, it has been reported that PwS show delayed paretic biceps femoris (BF) and bilateral RF onset latency and longer paretic and non-paretic interlimb coupling durations after externally induced balance disturbance (Marigold and Eng 2006; Tang et al. 1998). Additionally, several studies have shown that the ability to move the lower limbs rapidly depends on neuro-motor mechanisms related to the buildup of muscle force and power generation (de Kam et al. 2018), which is also diminished in PwS as consequence of reduction in muscle cross sectional area and impaired ability to recruit large amount of motor units (Marigold and Eng 2006). In our study we externally intervened both motor impairment (through a superficial stimulation of the paretic RF muscle with an amplitude range between 30 and 45 mA) (Table 5.2) and muscle onset latency (stimulating the muscle 50 ms after the perturbation onset) during a reactive balance task (Fig. 5.2 B). Our results showed that the application of NMES on the paretic RF reduced the laboratory falls incidence without differences in number of recovery steps (Fig. 5.3). In addition, results demonstrated improved stability values at the moment of the liftoff after the perturbation onset for slip-like perturbations (Fig. 5.4 A), and at the moment of the first TD after the perturbation (Fig. 5.4 C and 5.4 D) in both slip and trip-like perturbation trials compared to the experimental condition in which perturbations were delivered without NMES.

A plausible explanation for the improvements observed in the overall reactive balance strategy after slip and trip-like stance perturbations with the application of NMES on the paretic RF is that the duration of the stimulation included both the early and later phases of reactive balance control, covering the automatic stages of the reactive response as well as its late adjustments. Along these lines, several authors have described that the earliest part of the postural response after an external disturbance may not involve a cortical loop (Dietz et al. 1985; Jacobs and Horak et al. 2007), suggesting that the efferent path of the initial postural response is not properly timed with the afferent cortical potential in order to signify a transcortical loop (Ackerman et al. 1991; Payne et al. 2019), and that spinal cord and brainstem circuits are the main responsible of this early postural response (Dietz et al. 1985; Jacobs and Horak et al. 2007). Following this early phase of the postural response, studies have described that brainstem circuits and cortex become involved in shaping the postural reaction as the response progress, suggesting that a direct transcortical loop does not trigger the initial phase of postural responses to external perturbations but seems likely that the cerebral cortex becomes involved in later phases of the reactive balance control (Jacobs and Horak et al. 2007). This sequence of events requires an undamaged sensorimotor system that is, capable of responding to environmental demands quickly and with adequate timing to regain balance after a perturbation. This sequencing, is typically not observed in PwS who show difficulties to react with proper timing, thus forcing them to use compensatory strategies that limit their functionality after a loss of balance.

In the current study, we stimulated the RF of the paretic limb from 50 ms to 450 ms after the perturbation onset, which means that we intervened the muscle response of the group of muscles that most increases its activity during reactive balance strategies (Schumacher et al. 2019) during the early phase of the reactive response as well as in the later phase that include cortical control of the reactive reaction, which contributed to stabilize the support limb across most of the reactive balance response.

Regarding the functioning of the paretic limb during the reactive response, our result showed that the minimum hip height values of the paretic limb between the perturbation onset and the first TD were significantly higher when NMES was applied to the RF compared to the experimental conditions in which participants were exposed to stance perturbations without NMES (Fig.5.4 E and 5.4 F). These results were consistent with our hypothesis and confirmed that the application of NMES to the RF of the paretic limb contributed to prevent the limb collapse after a forward and backward balance disturbance by maintaining the knee extension in the support limb and at the same time preventing the descent of the hip that has been described as a limb collapse indicator (Salot et al. 2016; Wang et al. 2019). In line with other studies that have demonstrated that limb collapse is one of the most important factors that induce falls in population at high risk of falling (Wang et al 2019; Wang et al. 2020), our results showed that NMES applied to the RF of the support limb after stance perturbations contributed to maintain stability on the support limb. This, in turn, facilitated the unloading of the non-paretic leg and the transfer of the body weight from the non-paretic limb to the paretic limb after a balance disturbance, thus providing a more efficient execution of the stepping response with the non-paretic leg.

In concordance with the kinematic results observed in the paretic limb with the application of NMES, our results also showed that stepping initiation time (non-paretic limb) was significantly shorter when NMES was applied to the paretic RF during slip-like perturbation trials (Fig. 5.5 A). However, no differences in the step execution time (Fig. 5.5 C and 5.5 D) and step length (Fig. 5.5 E and 5.5 F) of the first recovery step was observed between NMES condition compared to the experimental conditions in which participants were exposed to stance perturbations without NMES. This reduced time in starting the recovery stepping helped the participants to regain the double stance position after a balance disturbance faster which allow us to infer that the use of longer step length became less important to regain stability after experience a slip. Additionally, a faster step initiation post-perturbation indicates that at liftoff (start of single stance) the participants were more stabilized compared to when the liftoff occurs with a delay after perturbation onset. In line with this interpretation, our results showed that at the moment of liftoff, MOS values were higher during the trials in which slip-like perturbations were synchronized with NMES compared to the trials without NMES (Fig.5.4 A). Thus, a faster step initiation time with a quick re-establishment of the double stance can provide a stabilization torque improving overall dynamic stability without necessarily having a longer step length.

5.5 Limitations of the study

The following limitations should be considered when interpreting the results of the current study. First, one important limitation of this study is the small sample size. A larger randomized controlled clinical trial is needed to confirm the benefits of NMES on the paretic limb of PwS during reactive balance control. Second, although all the participants included in this study presented hemiparesis, all of them were able to walk independently in the community. Further studies should test the current protocol in PwS with greater impairment in order to test whether less functional PwS can benefit from the intervention proposed in this study. Third, invasive intramuscular functional electrical stimulation has shown greater specificity in muscle stimulation, especially in deeper muscles, and more comfortable stimulation at higher levels compared to surface NMES. However, we decided to use surface NMES because it is a more available therapeutic tool in clinical facilities and also facilitates the replication of the present study protocol.

New NMES techniques for lower limb stroke rehabilitation continue to be developed, especially those that use sensors to trigger stimulation when PwS achieve some minimum volitional movement (Chung et al. 2014; Sabut et al 2010). However, it has been well described that any single NMES modality used in isolation from other sensorimotor rehabilitation therapies produce a substantial motor recovery in PwS. Therefore, there is a growing trend toward combining NMES with other emerging therapeutic strategies (Knutson et al. 2015). In the present study we combined a novel NMES technique that allows synchronization of a targeted electrical stimulation with an externally induced treadmill perturbation. To the best of our knowledge, this is the first study to describe the effect of NMES on reactive balance control after a stance balance disturbance in PwCS. According to our results, the inclusion of NMES to balance perturbation protocols appear as a valid therapeutic toll to enhance the efficacy of these protocols and, potentially, could allow the inclusion of PwCS with greater motor impairments to this type of externally induced balance perturbation protocols.

5.6 Conclusion

Our results showed that the application of NMES on the knee extensor muscles of the paretic limb reduces the incidence of laboratory falls and improves stability values and kinematic parameters associated with limb collapse after slip and trip-like perturbations in PwCS. These results could contribute to a better understanding of the role of the paretic limb on reactive balance control and could help develop new therapeutic strategies to improve reactive balance control in PwCS. Future studies may further demonstrate the efficacy of similar protocols in other populations who experience muscle weakness and balance problems, as well as in PwS with greater impairment.

Chapter 6

Effect of robotic-assisted training on gait in stroke participants: A case series

6.1 Introduction

Gait disorders in persons with chronic stroke substantially impact independence, quality of life, and fall-risk (Hsu, Tang, & Jan, 2003; Richards et al., 1993), making the restoration of independent and safe locomotion one of the most important aims in stroke rehabilitation (Bohannon, Andrews, & Smith, 1988). Previous traditional approaches to physical therapy have focused on improving motor function through task-oriented interventions, which have shown positive results in acute and the sub-acute stage of stroke recovery, but decreasingly so during the chronic stage (Richards et al., 1993).

There is growing evidence to suggest that a more recently developed therapeutic approach, termed impairment-oriented therapy (IOT), can improve motor function during the chronic stage of stroke recovery of even severely impaired individuals by inducing neuroplastic changes in the central nervous system (CNS) (Aisen, Krebs, Hogan, McDowell, & Volpe, 1997; Cordo et al., 2009; Forrester et al., 2011; Kwakkel et al., 2008). There are multiple types of sensorimotor impairments that affect limb movement after stroke and manifest as abnormal gait kinematics in the lower limb, including muscular weakness, spasticity, somatosensory loss, and co-contraction (Lin et al., 2006). Abnormal gait kinematics are an important indicator of lower limb impairment and disability after stroke (Bohannon, Andrews, & Glenney, 2013), however, the neurophysiological relationship between sensorimotor impairment and kinematic functions is not well understood. Physiological impairments in persons with stroke (PwS) compromise forward propulsion during gait by reducing walking speed, gait symmetry, and toe-clearance while increasing energy expenditure (Hsu et al., 2003). In addition to propulsion, strokes can affect ankle joint kinematics, which typically play an important role in maintaining balance while walking (Lin et al., 2006). In order to maintain balance while walking, a normal gait pattern requires coordinated activation of dorsiflexor and plantarflexor muscles (Lin et al., 2006), a minimum of 10 degree of active ankle dorsiflexion, absorption of body weight when the swing leg contacts the ground, as well as adequate forward propulsion of the body during the push-off phase (An & Won, 2016; Liu et al., 2008; Neptune et al., 2001). Thus, due to limited active ankle range of motion (ROM) and abnormal activation of the ankle dorsiflexors and plantarflexors, most PwS show an impaired heel strike, increased pronation, and/or increased knee hyperextension, resulting in a slow walking speed, reduced cadence, and shortened step length (An & Won, 2016).

Given the functional implications of neuromuscular and kinematic deficits of the ankle on gait, improving paretic ankle control during walking may help reduce the need of gait compensatory responses and improve the spatiotemporal parameters of gait in people with chronic hemiparesis. Previous research in PwS has shown that inclusion of specific active ROM training for knee and ankle joints improves functional gait parameters compared to functional approaches without targeted joint training (An & Won, 2016). Similarly, Kim and Eng (2003) showed that decreased isokinetic strength of the paretic ankle plantarflexors correlated with decreased gait and stair-climbing speed in PwS, confirming that lower limb neuromuscular impairments in PwS play an important role in abnormal gait kinematics (Kim & Eng, 2003).

Impairment-oriented therapy has become more amenable to clinic use due to advances in biomedical robotics which makes high-volume, repetitive training possible with the capacity to regulate intensity, record performances over time, and provide feedback in real-time (Forrester et al., 2011; Prange, Jannink, Groothuis-Oudshoorn, Hermens, & Ijzerman, 2009). Thus, therapeutic interventions that have combined robotic-assisted movement with biofeedback of active torque or electromyography (EMG) have been used to improve muscle strength and reduce hyperactive tone and involuntary co-contraction in upper and lower extremities (Cordo et al., 2009; Cordo et al., 2013). However, the efficacy of a robot-assisted IOT intervention on lower limb impairment, kinematics, and functionality, as well the interrelationship of these 3 hierarchical features of stroke recovery has not received as much attention as research on the upper limb (Hesse, Schmidt, Werner, & Bardeleben, 2003).

This case study reports findings from a 10-week robot-assisted training protocol applied to the paretic ankle of persons with chronic hemiparetic gait. The aim of this case study was to describe the potential benefits of robotic-assisted IOT applied to the paretic ankle of PwS on ankle impairment, kinematics, spatiotemporal parameters. We hypothesized that participants with chronic stroke would successfully complete thirty, 30-minute training sessions, 3 times per week for 10 weeks, and that the training would reduce impairments at the paretic ankle, improve interlimb coordination of the lower limbs, and improve spatiotemporal gait parameters, thereby enhancing overall gait function.

6.2 Methods

6.2.1 Case description

A sample of convenience consisting of 5 participants (3 males and 2 females) with chronic stroke (i.e., >6 months post-injury) was recruited to participate in a robot-assisted training program over 10 weeks, consisting of 3 training sessions per week. Prospective participants ages 18-85 were eligible for the study, and the mean age of those enrolled was 65.8±7.7 yr. The mean time post-stroke for the 5 participants was 96.0±113.6 months at enrollment (Table 6.1). Additional inclusion criteria consisted of a Fugl-Meyer Assessment of Lower Extremity score ranging from 6 to 23 and the presence of visible and/or palpable volitional contraction of the affected ankle dorsiflexor muscle. Candidate participants were excluded from the study if they had a bone density measurement with a T-score of <–2; a Modified Ashworth Scale spasticity score for the paretic ankle of >2; a score of <23 out of a possible 30 on the Mini-Mental Status examination; self-reported presence of any neurological disease other than stroke; acute musculoskeletal, cardiorespiratory conditions; or a Baclofen pump or Botox treatment within the last 5 months. No enrolled participant was undergoing any physical therapy at the time of enrollment, and all 5 participants were instructed not to start any new physical activity or physical therapy until the end of the study. Each participant used some type of assistive device for ambulation, completing 30 training sessions without any complications or adverse events. All participant has a normal or corrected to normal vision. The study protocol was approved by the University of Illinois at Chicago Institutional Review Boards. The Clinical Trials ID is: NCT01378637.

Participant	Age	Time since stroke (months)	Type of stroke	Stroke Location	Fugl-Meyer Assessment Lower Extremity
1	53	102	Hemorragic	Cortical	18
2	72	290	Ischemic	Cortical	21
3	66	46	Hemorragic	Cortical	11
4	72	10	Ischemic	Cortical	20
5	66	32	Ischemic	Cortical	14

Table 6.1. Participant Demographics and Stroke Traits

6.2.2 Intervention

The experimental design included 3 laboratory assessments and 30 sessions of ankle training using a novel robot-assisted motion training device (AMES Technology, Inc. Portland, OR) that has been previously employed in several studies involving PwS and those with incomplete spinal cord injury (Backus et al., 2014; Cordo et al., 2009; Cordo et al., 2013). The training device included 2 tendon vibrators, one for the tibialis anterior (dorsiflexor) tendon and the other one for the Achilles (plantarflexor) tendon; a graphical interface (computer and screen) to present visual feedback; and motor-control hardware and software to provide a cyclical ankle motion in the dorsiflexion and plantarflexion plane (Fig. 6.1).

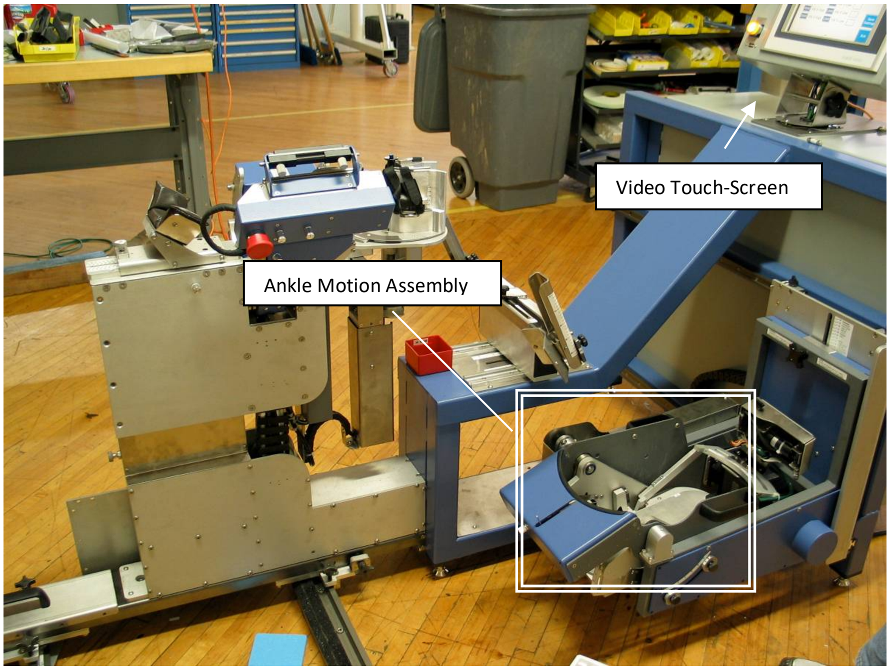

Figure 6.1. Interventional robot-assistive device.

All participants completed a total of 30 training sessions with a frequency of 3 sessions per week, each session lasting 30 min. During training, the ankle was ranged at 5 deg/s through an arc of ±15 deg, centered on the normal neutral position of the ankle. The participant's task was to assist the device in imposing the ankle motion by exerting volitional torque on the device in the same direction that the ankle was being rotated. A load cell mounted between the gearing and the ankle detected the total torque produced on the device's ankle fixture. During training, the software displayed only the participant's volitional contribution to total torque in real-time by subtracting the non-volitional component, which had been obtained during an earlier passive calibration trial. Volitional torque feedback was displayed during training along with a dorsiflexor or plantarflexor torque target set at ~25% of the participant's current strength in each direction. The trainer updated the dorsiflexion and plantarflexion torque targets during the 10-wk treatment period, which was typically an increase in the target. Participants were instructed during training to exceed the torque target and then to maintain a constant level of effort, even while their joint torque decreased due to fatigue or the length–tension properties of muscle.

At each reversal of movement direction, tendon vibration switched between the dorsiflexor and plantarflexor tendons to ensure that vibration was always being applied to the muscle(s) that were lengthening. Vibration was applied at 60 pulses/s, an amplitude of ~2 mm, and a background pressure of ~1–2 N. The participants wore a thin sock on the foot to decrease the friction between the Nylatron vibrator probes and the skin.

6.2.3 Assessments of impairments, kinematics, and function

Laboratory assessments were performed before the first training session ("baseline"), after the last training session ("post-training"), and 3 months after the last training session ("follow-up"). Each assessment included a customized gait test at a self-selected speed with and without an ankle-foot orthosis (AFO). In this test, each participant was asked to walk on a 5.12 m pressure floor mat (GAITRite, CIR System Inc., Franklin, NJ) at a self-selected comfortable walking speed. Three trials were performed with the participant wearing his/her AFO. Then, if the participant was capable, 3 trials were performed without the AFO. Each trial was separated by a 1-min rest period. Pressure sensors in the floor mat measured the temporal and spatial variables of gait. The system's gait analyzer generated and stored records to characterize each participant's spatiotemporal gait pattern. During the walking test, an inertial motion capture system (Xsens Motion Technologies, Enschede, Netherlands) recorded the lower limb joint angles of both the paretic and less affected ankles. MotionMonitor software (Innovative Sports Training, Inc, Chicago IL) was used to process and analyze these data.

In addition to the customized gait test, ankle strength was measured to provide an indication of overall impairment at that joint, since most sensorimotor impairments (e.g., neural/muscular weakness, spasticity, sensory loss, co-contraction) affect the overall strength at a joint. The strength test was performed with the participant in the interventional device. In contrast to the gait tests, strength was measured at the end of every training session (i.e., 30 times). In each strength test, the participant produced 3 maximal ankle dorsiflexions with a 5-10 s rest period between each effort.

6.2.4 Analysis

Due to the small number of participants and relatively high variability between them, no statistical analyses were conducted. Rather, we calculated average values of dependent variables and reported the percentage change from baseline. Average baseline measures were compared post-treatment as well as follow-up averages compared to baseline. Comparisons are reported as the differences in average values in percentages. Strength was not assessed during the follow-up assessment, so the overall change in strength for a given participant was based on the difference between baseline and post-training assessments.

6.3 Results

6.3.1 Effect of training on dorsiflexion torque and ankle range of motion during gait

After completing their training with the interventional device, participants showed an increase of 51.4% in dorsiflexion torque compared to baseline. Each participant's strength values are presented in Table 6.2.

Participant	**Baseline strength (N)**	**Post-training strength (N)**
1	124.66	195
2	16	156
3	54.66	30.66
4	16	100
5	73.33	76

Table 6.2: Dorsiflexion strength: A comparison across Pre-Training and Post-Training. **Abbreviations:** N: Newtons. Values are expressed as the average of 3 assessment performed before and after the training.

The peak ankle dorsiflexion angle achieved by participants during ambulation increased post-training, which subsequently reflected an increased ability to ambulate without an AFO (Table 6.2). Only two participants were able to walk without their AFOs during the baseline screening; however, at the end of the training protocol, 4 of the 5 participants were able to walk without an AFO. These training-induced effects on active dorsiflexion and the ability to ambulate without an AFO were retained 3 months after training. Although there was a slight decrease in dorsiflexion from the post-training to follow-up evaluations, the follow-up values remained higher than those from the baseline session. Peak values of dorsiflexion ROM during ambulation are presented for each participant in Table 6.2.

Participant	Baseline degree (º)	Post-training degree (º)	Follow up degree (º)
1	-6.92	4.03	2.01
2	-	4.01	1.21
3	-	-	-
4	-	3.13	1.03
5	-3.11	7	6.27
Means (SD)	-5.01±2.6	4.54±1.68	2.63±2.46

Table 6.3. Peak dorsiflexion ROM during gait. A comparison across Pre-Training, Post-Training, and Follow up assessments. **Abbreviations.** SD: standard deviations. Only 2 participants were able to walk without an AFO during the baseline assessment. And 4 participants were able to walk without an AFO after the training. Individuals values and means with standard deviations are presented across baseline, post-training, and follow up assessments.

6.3.2 Spatiotemporal gait parameters with AFOs

Training with the interventional device improved participants' spatiotemporal gait parameters when ambulating with their AFOs. All participants showed an increase in overall walking speed and cadence in the post-treatment compared to the baseline assessments, and these increases were retained by the follow-up assessments (Fig.6.2 A and 6.2 C). On average, participants showed a 28.7% increase in walking speed by the end of training compared to baseline and a 30.7% increase at the follow-up assessment compared to baseline (Fig. 6.2 A). Training was also associated with a 12% increase in cadence by the end of the training compared to baseline and a 10.5% increase at the follow-up assessment compared to baseline (Fig. 6.2 C).

Figure 6.2.

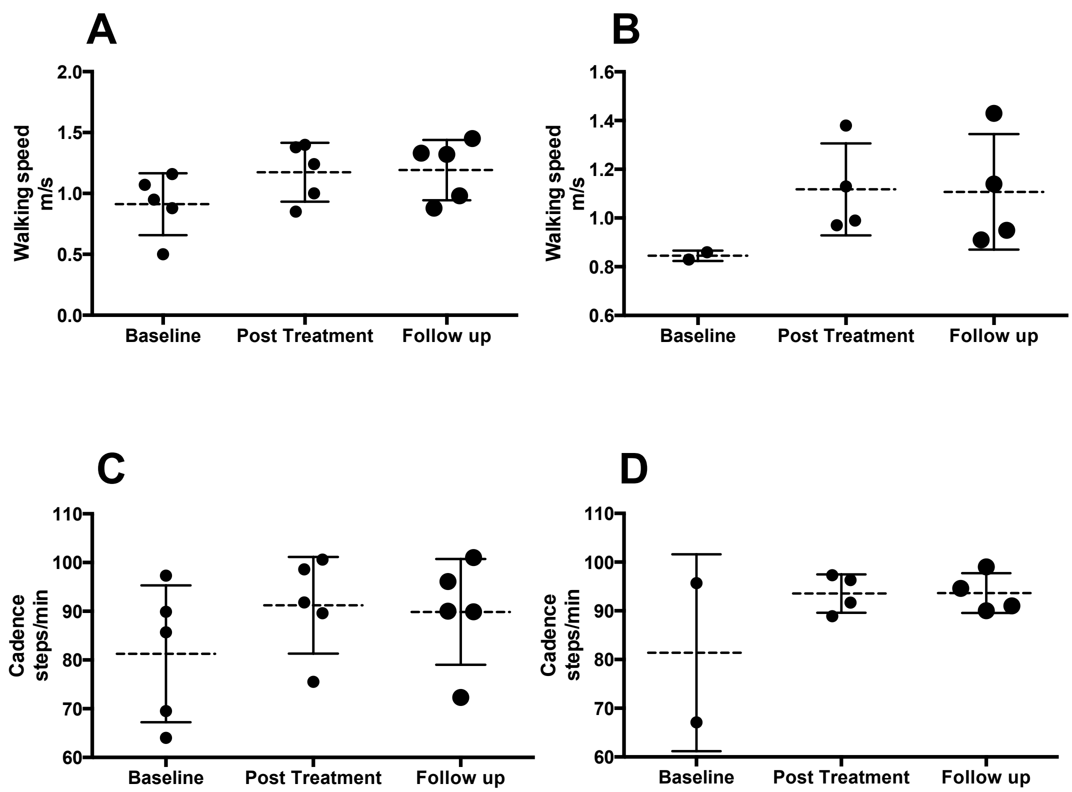

Figure 6.2. Effect of AMES therapy on gait spatiotemporal parameters A. Means and standard deviations of the walking speed with AFO during the baseline assessments, post-treatment assessment, and follow-up. **B** Means and standard deviations of the walking speed without AFO during the baseline assessments, post-treatment assessment, and follow-up. **C**. Means and standard deviations of the cadence with AFO during the baseline assessment, post-treatment assessment and follow-up. **D.** Means and standard deviations of the cadence with AFO during the baseline assessment, post-treatment assessment and follow-up. Each black dot represents values obtained for each individual.

Further, training with the interventional device was associated with several kinematic changes during gait specific to either lower limbs. In the paretic lower limb, the average percentage of the limb in support phase of the gait cycles was 27.4% higher at post-training compared to the baseline, and it was 31.7% higher than baseline at the time of the follow-up assessment (Fig.6.3 A). In the non-paretic lower limb, the step length was 30.1% greater at post-treatment compared to baseline, and it was 20.2% greater at the follow-up assessment compared to baseline (Fig.6.3 C).

Figure 6.3

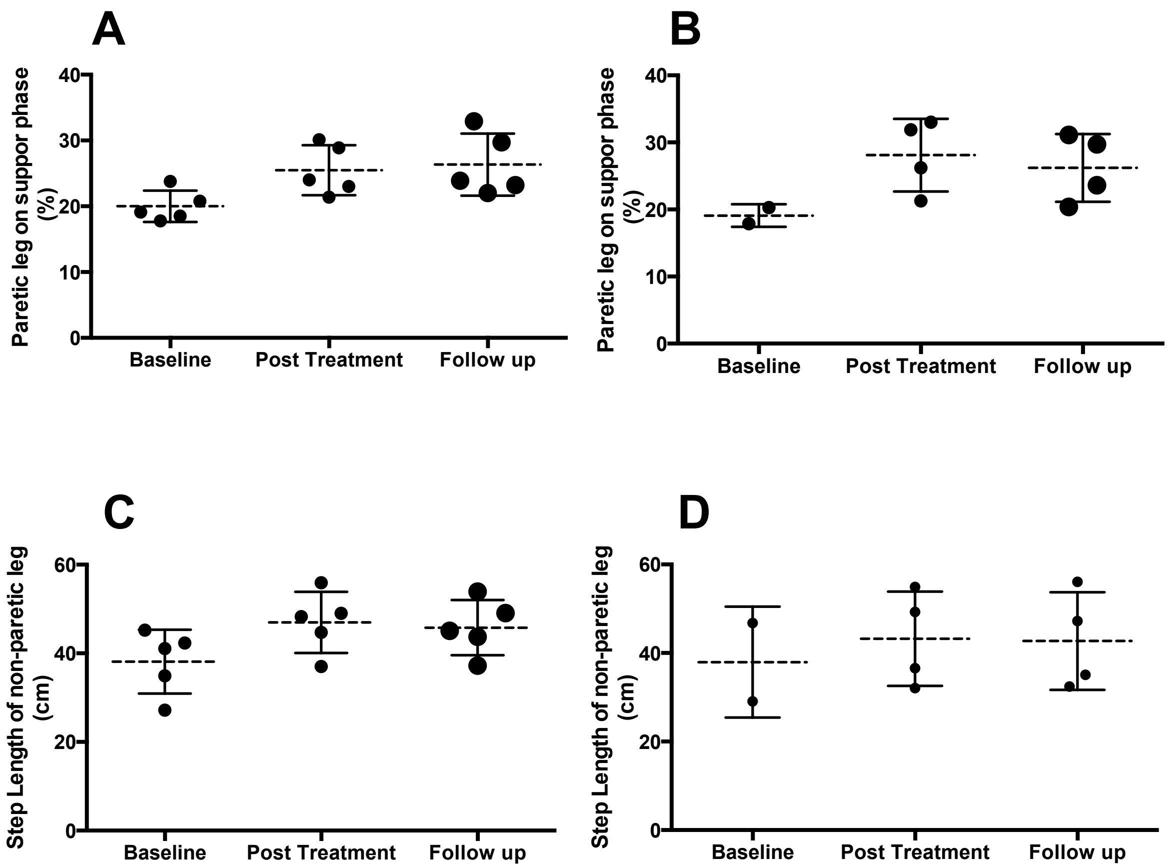

Figure 6.3. Percentage of the gait cycle in which paretic leg is in support phase and step length. A. Means and standard deviations of the percentage of the gait cycle in which the paretic leg is in support phase with AFO during the baseline assessments, post-treatment assessment, and follow-up. **B** Means and standard deviations of the gait cycle in which the paretic leg is in support phase without AFO during the baseline assessments, post-treatment assessment, and follow-up. **C** Means and standard deviations of the step length of the non-paretic leg with AFO during the baseline assessment, post-treatment assessment and follow-up. **D.** Means and standard deviations of the step length of the non-paretic leg with AFO during the baseline assessment, post-treatment assessment and follow-up. Each black dot represents values obtained for each participant.

6.3.3 Spatiotemporal gait parameters without AFOs

At baseline, only two participants (#1 and #5 in Tables 10-12) could walk without their AFO, and they both showed an increase in walking speed by the end of the training compared to baseline: in participant 1 from 0.83 to 0.97 m/s (#1) and in participant 5 from 0.86 to 1.38 m/s (Fig. 6.2 B). Both participants also showed an increase in cadence, with participant 1 increasing from 95.7 to 97.3 step/min and participant 2 increasing from 67.1 to 88.9 step/min (Fig. 6.2 D). Four participants were able to walk without an AFO by the post-training assessment with their average walking speed being 1.11 m/s. At the follow-up assessment, the average speed remained constant at 1.10 m/s (Fig. 6.2 B). Similarly, the average cadence of these 4 participants reached an average of 93.55 steps/min by the post-training assessment and remained constant at 93.65 steps/min by the follow-up assessment (Fig. 6.2 D).

The training also had an effect on the length of the paretic stance phase in participant 1 (from 20.3% to 21.3%) and in participant 5 (from 17.9% to 31.9%) when walking without their AFOs (Fig. 6.3 B). In addition, the step length of the non-paretic side also increased in participant 1 from 29.09 to 32.09 and in participant 5 from 46.8 to 54.90 (Fig. 6.3 D) at the post-training assessment relative to baseline. The average percentage of the gait cycle in which the paretic limb was in the support phase, for the 4 participants who could walk without an AFO, was 25.55% at the post-training assessment and 27.45% at the follow-up assessment (Fig. 6.3 B). The average step length of the non-paretic side in those who could walk without an AFO was 93.55 steps/min at the post-training assessment and 93.65 steps/min at the follow up screening (Fig.6.3 D).

6.4 Discussion

This case study provides evidence for potential benefits of robot-assisted training that targets lower limb impairment (i.e., IOT) in improving lower limb kinematics and, thereby, improving spatiotemporal gait parameters in persons with chronic stroke. This evidence, in turn, suggests that IOT can reduce paretic ankle impairments and potentially translate these improvements into increased functional mobility.

6.4.1 Effect of Impairment-oriented training on lower limb impairment, gait kinematics, and function

Although the contributions of specific impairments to weakness at the ankle joint (e.g., neural weakness, muscle atrophy, spasticity, contracture, co-contraction) were not differentiated in this study, the results showed that robot-assisted ankle rotation and feedback of the participant's assistive torque combined with antagonist muscle vibration led to a reduction in lower limb weakness and improvements in gait kinematics. We observed marked gains over the course of 30 training sessions in dorsiflexor torque (Table 6.2) and active dorsiflexion ROM in two of the participants who could walk without an AFO at baseline (Table 6.3). The other 3 participants were unable to walk without an AFO during baseline assessment, but 2 of them were later able to walk without it after all training was completed. Additionally, both participants who were able to walk without an AFO at baseline showed higher dorsiflexion peak angles during gait after the training compared to the baseline (Table 6.3). This improvement likely relates to the observed increase in dorsiflexion torque (Table 6.2). These results are consistent with previous studies describing the relation between lower limb muscle strength and gait performance in PwS.

Our results showed that, after receiving robot-assisted IOT to the affected ankle, participants' spatiotemporal and symmetry gait parameters improved (Fig. 6.2 and 6.3). Previous research suggests that gait asymmetry may be a key indicator for balance deficits and, consequently, risk of falls. Furthermore, gait asymmetry is associated with increased energy cost, risk of musculoskeletal injury, and loss of bone mass density in the non-paretic lower limb (Batchelor, MacKintosh, Said, and Hill, 2012). Lin, Yang, Cheng, and Wang (2006) reported that dorsiflexor strength and ROM in the paretic ankle is the primary determinant of spatiotemporal symmetry during gait. Limited ankle dorsiflexion increases the single-leg support time of the non-paretic leg and increases the swing time of the paretic leg, resulting in asymmetric gait (Lin et al., 2006). Improved ankle strength and ROM of the paretic ankle and the resulting increase in walking speed and cadence are also likely to contribute to improvements in stride length of the paretic leg. Further, these improvements increase the percentage of the gait cycle in which the paretic limb is in the support phase. By allowing the non-paretic limb adequate time in swing phase to execute a longer step, the symmetry of the gait pattern and functional mobility should also improve (Beyaert, Vasa, & Frykberg, 2015; Schwartz et al., 2009). Upon completion of all training sessions, all 5 participants showed an increase in walking speed and cadence during the walking trials with and without an AFO; however, these changes were less pronounced during the trials without use of an AFO than those in which the orthosis was used.

6.4.2 Muscle vibration and augmented proprioception

Muscle vibration is a potent and selective stimulus for muscle spindle Ia afferents (Burke, Hagbarth, Löfstedt, & Wallin, 1976a, 1976b), which are sensory receptors that provide the brain with a key source of proprioceptive input to control movement. Vibration has been shown to rapidly increase cortical somatosensory representations of the vibrated body part (Forner-Cordero, Steyvers, Levin, Alaerts, & Swinnen, 2008) and to improve motor coordination in PwS (Marconi et al., 2011; Noma, Matsumoto, Etoh, Shimodozono, & Kawahira, 2009; Paoloni et al., 2010). In the absence of proprioception, coordinated movement and motor learning are severely compromised, as seen in people with pan-sensory neuropathy (Gandevia & Burke, 1992). Mechanical vibration applied to a muscle at a stationary joint at frequencies between 30-70 pulses/s (Cordo, Gandevia, Hales, Burke, & Laird, 1993) can evoke simultaneous illusions of static joint displacement and continuous motion (i.e., velocity) (Gandevia & Burke, 1992) consistent with elongation of the vibrated muscle(s). During movement, if vibration is applied to a muscle while it is being elongated, the perceived displacement and velocity of motion is enhanced. The interventional device used in this study employs vibration during muscle lengthening as a means of selectively augmenting proprioceptive feedback of the assisted motion to the brain during training.

6.5 Conclusion and limitations

The results of this case study suggest that therapy addressing specific impairments underlying loss of lower limb function may be a useful therapeutic alternative to task-specific motor training, particularly for individuals with moderately severe to severe lower limb impairment. Our results further suggest that reducing impairments can lead to functional improvements such as gait spatiotemporal parameters and gait symmetry, which may subsequently improve gait stability as well as walking speed.

Although all the participants improved on most of the outcome measures reported in this case study (except strength tests and other assessments without an AFO for participant #3), we observed substantial variability across the 5 participants in their improvements in kinematic and spatiotemporal gait parameters. Therefore, additional research on a larger sample size are needed to confirm the findings reported in this case study.

Chapter 7

Conclusions

7.1 Conclusions

Postural control is no longer simply considered a summation of static reflexes, but rather a complex skill based on the interaction of dynamic sensorimotor and cognitive processes. Today, it is well established that postural control for stability and orientation requires a complex interaction of musculoskeletal and neural processes. Musculoskeletal processes include joint range of motion, spinal flexibility, muscle properties, and biomechanical components among linked body segments. On the other hand, neural processes, essential to postural control, include motor process, which include organizing muscles throughout the body into neuromuscular synergies, sensory-perceptual processes, involving the organization and integration of visual, vestibular, and somatosensory systems, and higher-level cognitive processes essential for mapping sensation to action as well as ensuring anticipatory and adaptive aspects of postural control.

Summarizing the series of studies presented in this thesis, we demonstrated that cognitive issues, such as mental fatigue, can impair postural control assessed during standing under varying sensory conditions in healthy older adults and in persons with stroke. Furthermore, mental fatigue affected balance control significantly more when participants were exposed to conditions in which there was proprioceptive disturbances. Additionally, we introduced and tested a novel computer-controlled moveable platform to induce slip- and trip-like perturbations during walking under varying sensory conditions, showing that the highest percentage of loss of balance and the lower stability values were observed in the conditions in which slip-perturbation trials were induced in combination with proprioceptive disturbances. Similarly, we demonstrated that this novel overground computer-controlled moveable platform was feasible to train reactive balance in older adults. Following the line of introducing and testing novel interventions to enhance reactive balance control, we also demonstrated that the application of neuromuscular electrical stimulation on the knee extensor muscles of the paretic limb reduces the incidence of laboratory falls and also improves stability values and kinematic parameters associated with limb collapse after stance slip- and trip-like treadmill perturbations. The results observed in this study contribute to a better understanding of the role of the paretic limb during reactive balance control and could help developing new impairment-oriented intervention strategies in order to improve reactive balance control in persons with stroke. Finally, we presented a case study that provides evidence for potential benefits of robot-assisted training that targets lower limb impairment (ROM, strength, and proprioception) in improving lower limb kinematics and, thereby, improving spatiotemporal gait parameters in persons with chronic stroke. This evidence suggests that impairment-oriented interventions can reduce paretic lower limb impairments and potentially translate to improved functional mobility.

Impairments of balance and gait leading to loss of mobility, falls, and disability are common occurrences for people with many neurological conditions and with older age. Much of our current understanding about balance control and its impairments has come from investigations of how healthy individuals and those with neurological disorders respond to situations that perturb balance control during voluntary tasks or in reaction to externally imposed challenges to stability. Knowledge obtained from these investigations has come from documenting the physical and physiologic characteristics of the perturbations together with the body's electrophysiologic, structural, kinetic, kinematic, and behavioral responses.

Impairments in the sensory, musculoskeletal, and central and peripheral nervous systems commonly seen in older adults and PwS can adversely affect the balance system, which requires a complex integration of many components. It is well known that balance dysfunction has serious implications on society because this is a major cause for falls, injury, and loss of functional independence in the elderly population and in those with neurological disorders. Similarly, it has been well described that balance problems are often multifactorial and require a multidisciplinary approach. Several treatment options including a variety of rehabilitation therapy approaches, assistive devices and equipment, medication for symptomatic relief, and even surgical interventions are available and can have positive effects.

In this thesis, we presented different perspectives on how to evaluate and treat balance control in older adults and in persons with stroke. Additionally, we studied the effect of task and impairment-oriented interventions on behavioral, kinematic, and neuromuscular components of balance and locomotion control, and we described the impact of cognitive fatigue on balance control in healthy older adults and in persons with stroke. Altogether, the series of studies presented in this thesis addressed the topics of reactive and volitional balance control, sensorimotor control, and cognition, and we proposed novel interventions to assess and treat risk of falling and locomotion in healthy older adults and in persons with stroke.

7.2 Future direction

Empirical evidence obtained with electrophysiological methods has provided strong arguments that aging and sensorimotor impairments are associated with a progressive shift in the reliance on spinal to supraspinal pathways (descending drive) to control leg muscle activity during standing, gait, and balance control. More specifically, aging and impaired nervous systems appear to decrease the contribution of group I afferent pathways from muscle spindles in the synaptic input received by the leg motor neuron pool through a strategy that favors the descending control of leg muscles and antagonist coactivation during gait and balance functions. Additionally, it has been well described that the cerebral cortex likely influences postural responses both directly via corticospinal loops and indirectly via communication with the brainstem centers that harbor the synergies for postural responses, thereby providing both speed and flexibility for pre-selecting environmentally appropriate responses to a loss of balance. Despite all of this evidence, the influence of the cerebral cortex on postural responses is still largely untested, and its influence may vary with context.

While anticipated losses of balance allow for the pre-selection and optimization of postural responses (Ackermann et al., 1991), the extent to which cortical preselection of postural responses also applies to entirely unexpected situations is unknown. Thus, for a truly unexpected loss of balance, the influence of cortical activity may include either online activation for selecting and optimizing an appropriate response, or pre-selection to allow for optimized responses based on prior experience and current context (sensorimotor integration). However, the occurrence of either of these options may further depend on the balance capability of the individual. In this context, a person with impaired balance may be incapable of rapidly selecting a context-appropriate response based on central set, and instead may depend on using cortical loops during the late phases of the response in order to shape the postural response to environmental demands. Thus, in addition to the basic physiological question of whether or not the cerebral cortex contributes to reactive balance control, further research is required to understand the role of the cerebral cortex in varying contexts. These contexts include changes that occur with dual tasking, altering the predictability of postural perturbations and/or the intentions of the person, and with age or disease. These open questions allow us to suggest that the next steps to follow in the study of gait and balance control in older adults and in persons with stroke are to examine the changes in the cortical activity during study paradigms such as the presented in this thesis, and from there, compare and corelate the behavioral, neuromuscular, and kinematic results observed in the aforementioned experimental paradigms with changes at the level of the cerebral cortex. Thus, with the current advances in neural imaging techniques, more attention should be paid to neurophysiological components of balance control in order to better direct physical, pharmacological, and surgical therapies for those with impaired balance and motor control.

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