THE EFFECTS OF GAIT RETRAINING ON MUSCLE COORDINATION AND FUNCTIONAL WALKING ABILITY POST-STROKE

by

Shraddha Srivastava

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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ABSTRACT

Stroke is a leading cause of serious long-term gait disability in the elderly. The central nervous system (CNS) is believed to use the abundant degrees-of-freedom (DOF) of muscles and joints in stabilizing a particular task variable important for task success such as footpath in walking, which may be altered following stroke. However, it is not known if the current gait training paradigms can improve the muscle or joint coordination during walking post-stroke. Furthermore, there is a lack of strong evidence supporting the effectiveness of one specific locomotion intervention for functional gait recovery after stroke. The overall goal of this study was to compare the effects of robot-aided gait training (RAGT) using an “assist-as-needed” paradigm with the body weight supported treadmill training (BWSTT) on functional walking ability and footpath coordination during walking post-stroke.

In the first aim I identified the role of groups of co-activated muscles (i.e., muscle modes) in stabilizing the footpath during walking in stroke survivors and their age and gender matched healthy controls, using the uncontrolled manifold (UCM) approach. Both healthy individuals and stroke survivors had a significantly greater mode variance that lead to a consistent footpath than mode variance leading to an inconsistent footpath. However, there were no significant differences between groups in the ability to stabilize the footpath. These results suggested that footpath is an important task variable during walking that is stabilized by the CNS in healthy and stroke population. In addition, stroke survivors may be able to stabilize their footpath equally well as healthy individuals.

The second and the third aims investigated whether there are differences in the effects of “assist-as-needed” RAGT versus BWSTT on improvements in gait parameters and footpath stabilization. I implemented a performance based RAGT which encourages subjects’ active participation and compared its effects with more widely used but labor intensive BWSTT. Subjects demonstrated improvements in their functional walking ability following RAGT and BWSTT evidenced by improvements in some of the gait parameters. Subjects receiving BWSTT also demonstrated improvements in their ability to stabilize the footpath. Though, no significant differences between the groups were seen, but RAGT may be used as an alternative gait rehabilitation method as it requires less physical effort of the therapists compared to BWSTT.

Overall this dissertation work suggested that healthy individuals and stroke survivors control their footpath during walking. Furthermore, the footpath stabilization and gait parameters can be modified following gait training. However, clear evidence regarding the superiority of one training paradigm over other is lacking, therefore future studies are needed to identify efficient strategies for gait rehabilitation post-stroke.

Chapter 1

INTRODUCTION

Stroke is a leading cause of serious long-term disability in the elderly. The functional status and quality of life of individuals decline following the occurrence of a stroke [1, 2]. Each year approximately 795,000 people experience a new or a recurrent stroke [3] and at 6 months post-stroke about thirty percent of the survivors need some assistance to walk [3, 4]. Walking ability in chronic stroke survivors is an important determinant of social participation and independence in activities of daily living [5, 6]. Therefore, gait disability leading to reduced functional independence and social participation can result in a decline in the quality of life post-stroke. However, locomotor rehabilitation results in an improvement in social participation as well as independence in the activities of daily living [7, 8]. *An effective and efficient method for rehabilitation of walking can help increase the quality of life of stroke survivors by improving the level of independence in daily living activities*.

1.1 Post Stroke Gait Disability

Most stroke survivors exhibit gait deviations, reduced gait velocity and gait asymmetries [9]. Some of the gait deviations include longer stance period of the non-paretic side [10] and an increase in the step width to compensate for the poor balance following stroke [11]. Weak plantarflexors and hip flexors during pre-swing resulting in reduced propulsive force can lead to an inadequate leg propulsion [12]. Additionally, stroke survivors frequently use compensatory strategies during walking. For example, during the swing phase there may be reduced dorsiflexion and or decreased knee and hip flexion that can result in reduced foot clearance. To prevent the dragging of the toes during swing phase the paretic limb may compensate by circumduction of the leg or hiking of the pelvis [9]. Reduced gait speed, gait abnormalities, and use of compensatory strategies can contribute to an energetically less efficient walking pattern in stroke survivors as compared to healthy individuals [11, 13-15].

Studies have suggested that energy expenditure decreases following gait rehabilitation in chronic stroke survivors [16]. Furthermore, individuals following stroke may have impaired muscle and joint coordination [17, 18] which may affect their walking pattern [19]. Therefore, for a more efficient gait pattern it is important to rehabilitate the gait of chronic stroke survivors using an effective training method. *Intensive gait retraining in stroke survivors may help in reducing the energy expenditure and improve coordination during walking.*

1.2 Current Methods for Gait Rehabilitation and Their Limitations

Numerous techniques have been introduced for gait rehabilitation after stroke. One of the techniques widely used is body weight supported treadmill training (BWSTT) [20, 21]. The BWSTT paradigm has been tested in both animals and human subjects and was found to be an effective method of gait rehabilitation following neurological impairments. Experiments performed on spinalized cats involved walking on the treadmill with the body weight supported by a belt around the thorax of the cats

[22]. With the progression of training, the cats progressively supported more of their body weight at different walking speeds. The cats receiving BWSTT demonstrated considerable recovery in their gait pattern compared to the cats with spontaneous recovery following the transection of the spinal cord.

Based on the results of the animal studies, a similar training paradigm was developed for human subjects with spinal cord injury [23]. Some recent literature supports BWSTT as an effective method of gait rehabilitation post-stroke, demonstrating an improvement in the comfortable walking speed, clinical measures, self-reported quality of life measures, spatiotemporal gait parameters, and bilateral coordination of the lower limb segments [20, 24-26]. An increase in corticomotor excitability has been reported to correlate with increased functional walking ability [26]. BWSTT has been shown to result in greater improvements in walking ability compared to the conventional physical therapy treatment in stroke survivors [21]. Conversely, a study with subacute stroke survivors by Duncan et al [27] suggests that a home-exercise program is as equally effective as BWSTT in promoting functional gait recovery. Thus, clear evidence for an advantage of BWSTT in gait rehabilitation post-stroke over other treatments is lacking.

An advantage of BWSTT is that it makes it easier for patients to control their lower limbs and trunk during locomotion, particularly in the early stages of recovery because it provides partial body weight support. This training is however, labor-intensive, as it requires at least two skilled therapists to manually assist movements of a patient's pelvis and impaired leg. It also does not provide a direct means to obtain objective measures of patient performance and improvement during training.

Recently, robot-aided gait rehabilitation has been developed to help address some of the aforementioned limitations of BWSTT. In recent years, various devices have been developed by different groups of researchers for the rehabilitation of neurological disorders of the brain and spinal cord [28-31]. One commercially available robotic device developed for gait rehabilitation is the Lokomat [30]. An active leg exoskeleton (ALEX) was developed in our laboratory that provides three degrees of freedom for trunk movement. This can be an advantage over the other devices for gait retraining, because restricting degrees of freedom of the trunk may limit improvements in trainees' gait patterns [32]. *Gait rehabilitation using a robotic exoskeleton has advantages over BWSTT by reducing therapist effort and allowing for online feedback and recording of performance. ALEX in particular has an additional advantage over other robotic devices with the extra degrees of freedom at the trunk that can enable a gait pattern comparable to walking over-ground.*

1.3 Gait Training Using a Robotic Exoskeleton With Performance Based Assistance

A recent development in robotic devices is the implementation of a compliant force field, which assists the subject as and when needed as an alternative to passively moving the limb through a prescribed target trajectory [31, 33]. The assist-as-needed paradigm is consistent with the basic feature of walking, which is the presence of some variability in the gait parameters from one step to the next even when the environmental conditions are fixed [34]. In addition, forcing the limb through a path using the prototype fixed force algorithm as opposed to an assist-as-needed algorithm can result in a person’s tendency to rely on the robotic assistance, and therefore reduce human effort [35]. Current literature suggests that both healthy and neurologically impaired individuals display increased muscle activity, heart rate, and human effort during walking using an assist-as-needed paradigm in comparison to a fixed force algorithm [36, 37]. Therefore, a paradigm with a compliant force field that permits step-to-step variability and promotes greater active participation of the trainee is likely to be more effective than a fixed force field training paradigm.

Reinkensmeyer [38] developed a computational model of sensory motor control to predict the best movement recovery comparing assist-as-needed and fixed assistance training paradigms. In addition to the increase in subject's effort [37], this model predicted that providing the assist-as-needed training paradigm will result in larger sensory motor recovery compared to fixed assistance. Moreover, studies in animal and neurologically impaired human subjects demonstrate that the assist-as-needed training technique has better effects on the improvement of gait parameters and muscle activation as opposed to continuous assistance [39-42]. In addition, a recent pilot study with a single stroke survivor demonstrated substantial improvement in ground reaction forces, clinical outcome measures, self-selected over-ground walking speed, and muscle coordination, or muscle mode organization (see Ting and Macpherson [43]), after receiving robotic gait rehabilitation using an assist-as-needed paradigm [44].

Recent studies used the assist-as-needed gait-training paradigm to temporarily modify the lateral malleolus path of healthy and neurologically impaired individuals [44, 45]. The assist-as-needed force field was used to guide the subject's malleolus path such that it closely matched the target malleolus path. Conversely, in some studies the assistance provided was based on the hip and knee joint velocities instead of a malleolus path [33, 46]. Research suggests that the central nervous system uses the abundant degrees of freedom of joint motions and muscles to stabilize variables more closely related to task performance [47], for example, the malleolus path for the task of clearing the foot during walking. Therefore, it may be more reasonable to provide a goal of training that is associated with stabilization of a particular task-relevant variable, such as the malleolus path instead of joint velocities. *Active participation by the subject using a compliant force field permits inherent variability in the movement and provides assistance as and when needed. This can lead to better recovery of the gait parameters in comparison to completely relying on the robotic exoskeleton for assistance. In addition, a training paradigm based on the feedback of a critical task-relevant variable may be more effective than a paradigm based on individual joint velocity feedback.*

1.4 Motor Recovery After Gait Rehabilitation in Stroke

Although some studies have demonstrated that robot-aided gait training can improve gait parameters in stroke survivors [44, 48], the mechanism of motor recovery is unclear. Researchers have attempted to identify the mechanisms underlying motor learning following robot-aided gait training [49-51]. Gait training with a Lokomat in healthy subjects has shown a decrease in short interval intracortical inhibition lasting for twenty minutes after the training suggesting changes in the excitability of cortical neurons [49]. Additionally, there is some evidence of increased muscle activity among neurologically impaired subjects following a robot-assisted gait training that was retained three months after the training [52]. This indicates that robot-aided gait rehabilitation can induce long-term changes in the muscle activation of neurologically impaired subjects. However, in the aforementioned studies, there is no information about whether or not these changes correlate with improvements in functional walking ability of the subjects. Furthermore, it has been suggested that functional recovery following gait rehabilitation in stroke survivors may not be correlated with improvements in the timing of muscle activation [53]. Therefore, studying just the amplitude and timing of EMG excitation may be insufficient to evaluate motor recovery.

Several researchers have proposed that the central nervous system (CNS) simplifies control in many cases by the grouping of multiple muscles into smaller units when performing functional tasks [43, 54]. These groups of muscles have been referred to as muscle modes, motor modules, or muscle synergies. An evaluation of the structure of muscle modes provides a better indication of the functional walking ability of stroke survivors than the Fugl-Meyer assessment scale [55, 56], which focuses on motor impairments. Therefore, to develop a better understanding of functional motor recovery following gait rehabilitation, in addition to the study of EMG activity, the establishment of muscle modes and their organization may provide a useful tool to evaluate the status and changes in motor impairments during locomotion. *Some evidence exists that robot-aided rehabilitation can alter muscle activation. To better understand motor recovery following gait training in addition to evaluating muscle activation, it is important to understand how the CNS controls the muscles in subjects with neurological injury and whether or not it is altered with training.*

1.5 Understanding The Neural Control of Muscles

The famous neurologist Hughlings Jackson [57] stated that "the CNS knows nothing of muscles, it only knows movements". A normal central nervous system (CNS) has an abundant number of potentially independent variables or degrees of freedom (DOF) available for motor control. This was first considered by Bernstein [58] as the degrees of freedom problem. Because there are more DOFs available than required to achieve a given motor task, the CNS has more than one solution available. The existence of muscle modes would tend to reduce the DOF "problem" at the muscle level. This can be achieved if the CNS only selects control signals that presumably would activate smaller number of neural networks than individual muscles, with each network activating an ensemble of different muscles. In other words, the number of muscles is likely to be greater than the number of muscle modes. As mentioned earlier, some studies have used the term motor module or muscle synergy to define the group of muscles being activated together [43, 59-61]. However, recently the term muscle synergy was defined as co-variation among a group of muscle modes that act to stabilize a particular task-relevant variable [54, 62-66], the latter aspect of the definition being crucial. This issue will be discussed further in this document in the section on synergies.

In contrast to the studies supporting the muscle modes as the unit controlled by the CNS, some recent studies have proposed that CNS controls individual muscles and not groups of muscles [67-69]. According to those studies, the identification of muscle modes using dimensional reduction methods reflects instead, task related or biomechanical constraints. Valero-Cuevas, Venkadesan [68] performed an experiment where the subjects were asked to produce different prescribed patterns of force with the index fingertip. EMG data were collected from seven muscles and subjected to dimensional reduction using principal component analysis. It was observed that the within trials variability did not support the presence of muscle modes. Most of the variance accounted for was within the first principal component followed by the second to seventh component, each of which had small percent of variance explained. Therefore, the study proposes that these results imply the presence of only one muscle mode for the given task. Based on these results they further suggest the possibility of CNS controlling individual muscle activities instead of muscle modes. However, force production with the index fingertip is a very simple isometric task, and it is possible that it does not require multiple muscle modes to accomplish this task. In another study, results from a cadaveric experiment demonstrated the presence of synergies during a finger force production task in the absence of a neural controller in a cadaveric human hand. This may suggest that the presence of muscle modes is attributed to task or the biomechanical constraints and not due to the preference of the CNS to control muscles in a lower dimensional space [69].

Conversely, a recent study argues that while studying the neural control at the level of muscles, the directional tuning of the muscle activation (i.e. the activation of muscles associated with force production in a certain direction) has not been considered in either of the aforementioned studies [70]. Based on the results of Borzelli, Gentner [70] the directional tuning of activation of muscles predicted from using the muscle mode data matched the experimental data more closely compared to the predictions using the individual muscle activation data. Therefore, they suggest that the CNS controls muscle modes and not individual muscles to perform a task. Additionally, studies supporting neural control at the level of individual muscles have been limited to isometric finger force production; therefore there is a need to further investigate this issue in a larger set of activities. A study performed on animals supports the hypothesis that the CNS controls muscle modes [71]. Discharge from neurons in the arm area of the primary motor cortex and muscle activity of the trunk, shoulder, arm, and hand were recorded from monkeys during a reaching movement. The results revealed that the neuronal discharges from individual neurons in the primary motor cortex were strongly correlated to the activity of muscle modes required to perform the movement while correlations between a single muscle's activity and individual neuron's firing were not very strong. Furthermore, a study by Neptune, Clark [72] demonstrated that the biomechanical outputs in a muscle driven simulation of walking were consistent with the results from a muscle mode actuation model. This suggests that a less complex neural control with fewer variables to control can produce a well-coordinated walking pattern. This feature of the CNS is retained even when a perturbation is introduced to the system during walking [73]. Therefore, it is reasonable to conclude that in many tasks there is a high probability that the control signals from the CNS activate groups of muscles rather than individual muscles. *The CNS provides input to the muscles in groups referred to as muscle modes in non-neurologically impaired individuals.*

1.6 What is a Synergy?

The term synergy has been used frequently in the past in different contexts. The word synergy means working together. Recently, in the field of motor control, synergy has been defined by Latash [74] as:

> "A task specific covariation of elemental variables in order to stabilize a certain task variable across repetitions"

This would mean that the synergy is a structural unit such that the elements of the unit or elemental variables work together for a task specific goal such as maintaining the stability of a task variable. If one of the elements of the structural unit makes an error, the other elements compensate to achieve the desired output. Synergies can be understood better using the classic example of finger force production stated by Latash [74]. If the goal is to produce a force of 10N by pressing with two fingers such that the force produced by finger 1 (F1) + the force produced by finger 2 (F2) =10N, then there are infinite combinations of F1 and F2 that can achieve this result. An individual could produce an equal amount of force with both fingers. However, when a person is asked to perform the same task multiple times one of the fingers may produce a larger force say for example 7N, requiring the other finger to compensate for the large force by producing only 3N. This suggests that the two fingers are working together in a synergy to produce a force of 10N. Therefore, error compensation is an important feature of a synergy.

A computational approach, the uncontrolled manifold (UCM) method, was developed to understand different roles of motor variability [47] and their relationship to stability of task-relevant variables. The approach provides a framework for evaluating the presence or absence or the strength of a synergy. The UCM hypothesis assumes that for a given task, variables more closely associated with task success can be identified (i.e., task-relevant variables). The CNS is hypothesized to define a subspace of the elemental variables (e.g., muscle modes) within which combinations of those variables provide for task flexibility without affecting the stability of the task-relevant variable. Thus, two orthogonal subspaces can be defined in the space of motor elements. The subspace within which the variability of the elemental variables does not affect the desired value of the task variable is the uncontrolled manifold and variability of motor elements within that subspace has been referred to as “good” variability or V_{UCM}. Variability of the motor elements within the subspace orthogonal to the uncontrolled manifold has been referred to as “bad” variability, or V_{ORT}. Only “bad” variability, or V_{ORT} will affect the desired value of the task variable [75]. In postural studies muscle modes were shown to be scaled in a flexible manner across repetitions, reflecting muscle synergies that stabilize the center of pressure position in various postural tasks [54, 63, 64]. Identification of the muscle synergies in walking using the UCM approach has not been addressed in previous literature. *The CNS utilizes its abundant degrees of freedom by forming muscle synergies that help to produce stable values of task-relevant variables in a flexible manner. A computational approach called the UCM approach has been used to understand the muscle synergies.*

1.7 Muscle Modes and Muscle Synergies During Walking in Stroke

Healthy individuals have been shown to exhibit four to five muscle modes during walking [17, 72, 76]. The structure of these modes was consistent across different speeds of walking. However, there is evidence that there is an alteration in the number and activation profile of muscle modes following a stroke [17, 77]. The number of modes have also been shown to correlate with the level of motor impairment [55]. There can be a smaller number of muscle modes following stroke within the paretic limb as compared to the non-paretic limb and to healthy individuals. This may be the result of an impaired ability of the CNS to independently control these modes [17]. These alterations in the muscle modes may be associated with alteration in the control of the task-relevant variables or muscle synergies during walking.

Falls are a major health concern in stroke population [78]. Furthermore, fear of falling may restrict the activities of daily living of an individual [79]. Foot position is considered as an important task variable by the nervous system to maintain balance during walking [80]. One of the most common causes of falls during walking is reported to be tripping [81]. An important predictor of falls is foot clearance during swing phase [82], and it's decrease results in an increase in the risk of falls due to trips [83]. Furthermore, as mentioned previously in this document, stroke survivors may have a lower foot clearance due to reduced dorsiflexion or decreased knee and hip flexion [9]. Therefore, adequate foot clearance is critical to avoid falls during walking [84, 85]. Consequently, understanding the control of the foot in the vertical direction during the swing phase of gait is important. Furthermore, elderly fallers have demonstrated shorter step length than non-fallers [86]. Recent research has been done to understand the use of motor abundance to control the foot in the medio-lateral direction during walking in healthy individuals [87]. To our knowledge, no studies have been performed to date to understand the role of muscle synergies in controlling the vertical or antero-posterior foot position during walking. As mentioned previously, looking at the activation timing and amplitude of muscles during walking may not be enough for evaluation in stroke survivors. Therefore, understanding the muscle synergy [75] during walking in healthy persons as well as stroke survivors can provide additional information about stabilization of foot position important for avoiding falls.

Practice can lead to changes in the composition of muscle modes [88, 89]. Asaka, Wang [88] demonstrated the effect of practice on muscle modes in healthy individuals.

Subjects were asked to perform a load release task while standing on an unstable board. A change in composition of muscle modes was observed from before to after five days of practice. Additionally, UCM analysis revealed the emergence of muscle synergies stabilizing the center of pressure position during the experimental task with practice. Another study done with stroke survivors demonstrated slight changes in the muscle modes after 36 sessions of BWSTT [89]. The composition and the timing of the modes of stroke survivors were compared with age matched healthy individuals. The results from the study supported their hypothesis that training can result in changes in muscle modes such that they resemble the modes of healthy individuals more closely. Therefore, practice may lead to changes in muscle modes in neurologically impaired subjects. To our knowledge there are no studies that have investigated the effect of training on the muscle synergies, as defined by Latash, Scholz [75] during walking in stroke survivors. Comparing the effect of assist-as-needed training (RAGT) with BWSTT on the muscle modes and muscle synergies during walking may help us gain better insights into the underlying mechanisms of motor learning following gait retraining and how it differs, if at all, with different training approaches. *Studying the muscle modes and the coordination of modes in stabilizing the foot position during walking in healthy individuals and stroke survivors can help us identify and compare the effects of RAGT with BWSTT on the neural control of foot position that is important to minimize falls.*

1.8 Specific Aims

Impaired balance during walking and high incidence of falls is often demonstrated in stroke survivors. One of the most common causes of falls during walking is tripping due to inadequate foot clearance. The nervous system controls foot trajectory during the swing phase of walking in healthy individuals to maintain stability and minimize falls due to trips. However, there is a lack of understanding regarding the footpath control in stroke survivors. The central nervous system is believed to use the available flexibility provided by its abundant degrees-of-freedom to co-vary muscles and joint motions involved in stabilizing a variable important for task success, such as footpath in walking. Previous literature suggests that the CNS controls muscles in a smaller number of groups termed muscle modes instead of controlling individual muscle activation during a task. These muscle modes are scaled in a flexible manner across repetitions to stabilize a variable important for task success. This flexible scaling of muscle modes related to stabilization of a task variable is considered a muscle synergy. The purpose of our first study is to investigate the role of muscle synergies in stabilizing the footpath during swing in stroke survivors and healthy individuals. Gait rehabilitation post-stroke is important as it leads to a more efficient walking pattern, improvement in social participation, and independence in the activities of daily living. BWSTT is a widely used method for gait rehabilitation post-stroke. However, this method is labor intensive and requires one or more therapists for manual assistance. Furthermore, clear evidence for the effectiveness of BWSTT post-stroke is lacking. To help address the limitations of BWSTT, robot-aided gait rehabilitation has been developed recently. The current robot-aided training (RAGT) paradigm provides continuous assistance that substantially reduces the subjects' effort. Therefore, a novel assist-as-needed paradigm using a robotic exoskeleton has recently been developed. An assist-as-needed paradigm allows step-to-step movement variability and encourages subjects' active participation. <u>*The overall goal of this study is to gain a better understanding of*</u>

the foot position control post-stroke and to compare the effects of BWSTT with assist-as-needed RAGT on gait parameters and neural control of footpath. This information can help us in optimizing gait rehabilitation strategies to improve functional walking ability and minimize falls.

Aim 1: To determine the extent to which the across-cycle variance of muscle modes during swing reflects the flexible scaling of the magnitudes of muscle modes to produce a consistent (V_{UCM}) or variable (V_{ORT}) swing phase footpath, and how this differs between stroke survivors and age-matched control subjects without a neurological disorder.

Hypothesis 1.1: *V_{UCM} will be significantly larger than V_{ORT} in control subjects without a neurological disorder.*

Hypothesis 1.2: *Stroke survivors will exhibit a similar behavior with $V_{UCM} > V_{ORT}$ as the control subjects, although ratio of V_{UCM} to V_{ORT} will be smaller in persons with stroke compared to non-disabled individuals, revealing greater difficulty in stroke survivors of dissociating muscle mode combinations that allow for flexibility from those that lead to footpath variability.*

Hypothesis 1.3: *Based on the Fugl-Meyer assessment scores, stroke survivors with a greater impairment level will have fewer muscle modes compared to the less impaired subjects.*

Aim 2: To identify the effects of robot-aided gait training using an "assist-as-needed" paradigm on stroke survivors' over-ground walking performance.

Hypothesis 2.1: *Stroke survivors' will exhibit improvements in their gait parameters and clinical scores following training.*

Hypothesis 2.2: *The changes in the gait parameters and clinical scores will be retained six months following training.*

Aim 3: To investigate the extent to which robotic gait retraining versus BWSTT in stroke survivors leads to changes in functional walking ability, groupings of muscles in muscle modes, and the muscle synergies stabilizing the footpath during the swing phase of over-ground walking.

Hypothesis 3.1: *The contribution of muscles within modes and the activation of modes during the gait cycle will change towards that of control subjects following robotic gait retraining and BWSTT.*

Hypothesis 3.2: *The ratio of V_{UCM} to V_{ORT}, gait parameters, and clinical scores will improve regardless of the training method.*

Hypothesis 3.3: *Greater improvements in ratio of V_{UCM} to V_{ORT}, gait parameters, and clinical scores following training will be seen in individuals receiving assist-as-needed robotic training in comparison to BWSTT.*

Chapter 2

COORDINATION OF MUSCLES TO CONTROL THE FOOT POSITION DURING OVER-GROUND WALKING IN HEALTHY INDIVIDUALS AND STROKE SURVIVORS

2.1 Abstract

The central nervous system (CNS) is believed to use the abundant degrees-of-freedom (DOF) of muscles and joints in stabilizing a particular task variable important for task success, such as the footpath in walking. In the current study we use the uncontrolled manifold (UCM) approach to understand the role of motor abundance in stabilizing the footpath during the swing phase of walking in healthy individuals, and in stroke survivors. Persons with hemiparesis following stroke often demonstrate impaired balance during walking and high incidences of falls due to inappropriate foot placement. The UCM approach determines how the variability of joint motion or muscle activation resulting from the abundant DOF is related to the variability of footpath across trials. In the current experiment twelve stroke survivors and their age and gender matched healthy controls walked over-ground at their self-selected speed while their electromyographic and kinematic data were collected. UCM approach was used to partition the variance of muscle groups (modes) across gait cycles into two components. (1) Muscle mode variance that leads to a consistent or stable footpath and, (2) muscle mode variance that leads to an inconsistent footpath. Both healthy individuals and stroke survivors had a significantly greater mode variance that lead to a consistent footpath than mode variance leading to an inconsistent footpath.

However, there were no significant differences between groups in the ability to stabilize the footpath. These results suggest that footpath is an important task variable during walking that is stabilized by the CNS in healthy and stroke population. Furthermore, stroke survivors' ability to stabilize the footpath following stroke may be similar to healthy individuals.

2.2 Introduction

Falls are a major health concern in healthy elderly and individuals with neurological disorders [90-92]. An increase in fall incidents with age has been reported [93]. Furthermore, people may be at a higher risk of falls due to gait and balance impairments and sensorimotor deficits following neurological injuries, stroke being the second most common condition [90]. It has been reported that 73% of stroke survivors have one or more fall incidents within 6 months of discharge from the hospital [78]. Majority of falls occur during walking in the community dwelling elderly and stroke population [91, 94]. Therefore, fear of falls during walking may restrict the activities of daily living and social participation of an individual [79]. This can further lead to deterioration in gait parameters including reduced gait speed, reduced stride length, and increase in double support time [95]. Falls can also lead to serious injuries such as hip fracture which can further reduce mobility [96-98], and often requires surgery and rehabilitation resulting in high healthcare costs and decline in the quality of life [93]. Therefore, prevention of falls is important for community dwelling elderly people and stroke survivors.

Tripping during walking is reported to be the most common cause of falls in the healthy elderly population [81, 94] and in individuals with neurological disorders [90]. Falls due to trips may be a result of inadequate foot clearance [78, 82, 99].

Furthermore, elderly fallers have demonstrated shorter step length than non-fallers [86]. Recently maximum step length has been used as a clinical measure to identify fallers such that reduced step length correlates with increased risk of falling [100, 101]. The four square step test used to evaluate dynamic balance also implicates step length and foot clearance as important determinants of falls [102, 103]. Therefore, adequate foot clearance and step length are important to minimize the risk of falls during walking. Stroke population frequently exhibits lower-extremity motor impairments. Individuals may exhibit reduced dorsiflexion and or decreased knee and hip flexion during the swing phase that can result in reduced foot clearance post-stroke [10]. Furthermore, stroke survivors may also have reduced strength of hip and knee extensors and ankle platarflexors [10] which has been associated with a decrease in step length [104, 105]. These altered gait patterns may increase the risks of falls post-stroke.

Previous studies have looked at the step-to-step variability of various gait parameters such as step length, step time, and step width to predict falls in healthy young and older adults during walking [80, 106]. Some studies have suggested that an increase in variability of foot clearance during swing is a predictor of falls [82, 83]. Disorders of the nervous system such as stroke and Parkinson’s disease are associated with greater step-to-step variability [107, 108]. However, there is a lack of information regarding the role of the central nervous system (CNS) in optimizing the variability of gait parameters or task variables such as footpath to minimize falls. The CNS is provided with more degrees-of-freedom (DOF) than necessary at the level of joints as well as muscles to perform a task [58]. The computational method of uncontrolled manifold (UCM) approach allows us to understand how the CNS uses the variability of joint motions or muscles' activation across cycles to stabilize a task variable [47, 109] , for example the footpath in walking which is an important variable controlled by the CNS [110]. According to the UCM approach the variance of the joints or muscles across gait cycles can be divided into two components. The variance that leads to a stable footpath is termed "good variance" or V_{UCM} and the variance component that results in a variable foot position is termed as "bad variance" or $V_{ORT.}$ Therefore, a greater V_{UCM} in comparison to V_{ORT} will suggest that a larger portion of the joint or muscle variance across cycles is contributing towards a stable footpath. The strength of this stabilization is determined by the relative variance difference which is the difference between the two variance components divided by the total variance [111].

It has been suggested that a hierarchy of synergies to control a task variable may exist [112]. A recent study suggested that CNS uses joint variability across gait cycles to stabilize footpath in the medio-lateral (ML) direction. However, there is no previous study that has looked at the higher level of hierarchal control, i.e. variability of the muscles' activation across cycles to stabilize the footpath. Recent studies have suggested that the CNS does not control individual muscles, instead the muscles are controlled in groups called muscle modes [43, 54]. The purpose of the current study was to identify the distribution of good and bad muscle mode variance used to stabilize the vertical and AP footpath across cycles during swing in the stroke population and age matched healthy controls. We hypothesized that the good variance (V_{UCM}) would be larger than the bad variance (V_{ORT}) in both healthy and stroke individuals. However, the total amount of variability used by the stroke survivors would be much larger than the total variability across cycles in the healthy elderly population. In addition, the relative variance difference would be higher in the healthy individuals in comparison to the stroke survivors suggesting a greater stability of the footpath.

2.3 Methods

2.3.1 Subject Information

Twelve Stroke survivors (9 males, 3 females) who had sustained a stroke more than 3 months prior to the study were recruited. Demographic details of the stroke survivors are listed in Table 2.1. Subjects were excluded if they had evidence of multiple strokes, chronic white matter disease on MRI, congestive heart failure, peripheral artery disease with intermittent claudication, cancer, pulmonary or renal failure, unstable angina, uncontrolled hypertension (> 190/110 mmHg), dementia (Mini-Mental State exam < 22) [113], severe aphasia, orthopedic conditions affecting the legs or the back, or cerebellar signs (e.g., ataxia). Non-neurologically impaired gender matched control subjects were recruited whose age was within +/- 5 years of each stroke survivor's age. Control subjects were included only if they were free from any musculoskeletal, vascular, or neurological disorder that can significantly affect their walking ability. All subjects gave written informed consent to participate in the study, approved by the University's Institutional Review Board.

Table 2.1. Demographic Details of the Stroke Survivors.

Subject ID	AGE (yrs)	Duration Post-stroke (months)	Side affected	Gender	Number of Modes	Fugl-Meyer Assessment
S1	56	95	Left	M	4	24.00
S2	80	53	Left	M	4	25.00
S3	60	3	Right	F	3	11.00
S4	43	3	Right	M	4	21.00
S5	67	20	Left	M	4	12.00
S6	70	149	Left	F	4	28.00
S7	58	17	Left	M	4	24.00
S8	48	11	Right	F	4	27.00
S9	75	14	Right	M	3	17.00
S10	54	12	Left	M	4	17.00
S11	59	35	Left	M	4	24.00
S12	59	3	Right	M	4	17.00

2.3.2 Data Acquisition and Analysis

Stroke survivors and healthy controls were asked to walk at their self-selected over-ground walking speed (Table 2.2). Kinematic data were recorded from all the subjects at a sampling frequency of 120-Hz using an eight-camera Qualisys (Gothenburg, Sweden) motion capture system. Electromyographic (EMG) data from ten muscles were recorded using a 16-channel EMG system (MA-416-003 Motion Lab System Baton Rouge, LA) at a sampling frequency of 1200 Hz with a 16-bit resolution. Disposable self-adhesive surface electrodes were used on the muscle belly of the biceps femoris longus, vastus lateralis, vastus medialis, rectus femoris, gluteus medius, soleus, medial head of gastrocnemius, lateral head of gastrocnemius, semitendinosus and tibialis anterior muscles. To obtain a linear envelope, the EMG signals were high pass filtered with a cutoff frequency of 20-Hz, rectified, and then low pass filtered with a cutoff frequency of 6-Hz using a second order Butterworth filter. EMG from each muscle was normalized to its peak amplitude across all gait cycles. Footpath during swing phase was based on the coordinates of the reflective marker attached on top of the fifth metatarsal of the paretic foot. Marker trajectories were low pass filtered with a cutoff frequency of 6-Hz. The EMG data and the marker coordinates were used for UCM analysis involving three major steps.

Step 1: Non-negative matrix factorization

The first step involved computing the muscle modes. The normalized linear envelope was used for computation of muscle modes using the non-negative matrix factorization (NNMF) [43]. EMG data from all the gait cycles was concatenated together to compute muscle modes across time. NNMF factors the concatenated original EMG data (V) into two matrices.

Table 2.2. Self-selected Over-ground Walking Speed of Stroke Survivors and Healthy Individuals.

Stroke Survivors	**Self-selected Speed (m/s)**	**Healthy age and gender matched controls**	**Self-selected Speed (m/s)**
S1	1.04	C1	1.11
S2	0.75	C2	0.94
S3	0.15	C3	0.98
S4	0.53	C4	1.04
S5	0.29	C5	1.11
S6	0.78	C6	1.13
S7	0.55	C7	1.03
S8	0.67	C8	0.98
S9	0.16	C9	1.14
S10	0.54	C10	1.01
S11	0.90	C11	0.98
S12	0.55	C12	1.09

The matrix W corresponds to the mode structure, and specifies the relative contribution of each muscle to a muscle mode and the matrix H is the activation timing of each muscle mode across a gait cycle. The number of adequate modes required for reconstructing the original EMG after data reduction was based on variability accounted for (VAF). VAF was computed as the sum of squared errors divided by the sum of squared original data as shown in equation (1).

$$VAF = \frac{1-\left(V-(W\times H)\right)^2}{V^2} \tag{1}$$

The analysis starts with the assumption that only one mode is sufficient to reconstruct the EMG data. The number of modes was increased until a VAF > 90% was achieved for each of the ten muscles [17].

Step 2: Linear Regression

To determine how changes in the modes (ΔH) are related to the changes in the footpath (ΔFoot) during swing phase, regression analysis was used. The regression equation for the changes in the vertical position of foot during swing phase related to changes in the muscle modes was given as equation (2):

$$\Delta Foot_z = C_{1z}\Delta H_1 + C_{2z}\Delta H_2 + C_{3z}\Delta H_3 + C_{4z}\Delta H_4 \tag{2}$$

The equation for the AP position of foot was given as equation (3):

$$\Delta Foot_{AP} = C_{1AP}\Delta H_1 + C_{2AP}\Delta H_2 + C_{3AP}\Delta H_3 + C_{4AP}\Delta H_4 \tag{3}$$

Here C_1, C_2, C_3, and C_4 are the regression coefficients in case of four modes. The coefficients were computed at each sample across multiple time-normalized gait cycles used to compute the Jacobian (J) = [C_1, C_2, C_3, C_4].

Step 3: Uncontrolled Manifold Analysis

The Jacobian matrix was used for further analysis to compute how much of the muscle mode variance leads to variability of the footpath (V_{ORT}) or reflects flexible combinations of the muscle modes that produced a consistent footpath (V_{UCM}) using the uncontrolled manifold (UCM) approach [47]. We computed the null space of the

Jacobian (ε), which represents changes in the modes that lead to a consistent footpath. This null space is defined as the UCM subspace. The DOF for the UCM subspace is n-d where n is the number of modes. The foot path accounts for two DOF (d) for the vertical and AP positions. The mean-free mode data ($\Delta H_{mean\ free}$) was projected into the UCM subspace (equation 4):

$$UCM = \sum_{i=1}^{n-d} \left(\varepsilon \times \ \Delta H_{mean\ free}\right) \tag{4}$$

and orthogonal subspace (equation 5):

$$ORT = \left(\Delta H_{mean\ free} - \varepsilon^T \times UCM\right) \tag{5}$$

The variance in the UCM subspace (V_{UCM}) was computed per DOF at each data point averaged across all gait cycles (N) (equation 6):

$$V_{UCM} = \frac{1}{N}\frac{1}{n-d}\sum_{i=1}^{N}(UCM^2) \tag{6}$$

Variance in the subspace orthogonal to the UCM space, or V_{ORT}, was computed at each data point per DOF of the orthogonal space (d) (equation 7):

$$V_{ORT} = \frac{1}{N}\frac{1}{d}\sum_{i=1}^{N}(ORT^2) \tag{7}$$

The relative difference (ΔV) between the two variance components is computed (equation 8)

$$\Delta V = \frac{V_{UCM} - V_{ORT}}{V_{UCM} + V_{ORT}} \tag{8}$$

ΔV with a value close to positive one suggests greater ability of an individual to stabilize the footpath. The total variance (V_{TOT}) for all the subjects during swing phase is given as equation (9):

$$V_{TOT} = \frac{(V_{UCM} \times n) - \left(V_{ORT} \times (n-d)\right)}{(n+d)} \qquad (9)$$

For statistical purposes, the average of variance components, total variance, and relative variance difference is taken across the swing phase for each subject.

2.4 Statistical Analysis and Results

A mixed design ANOVA was performed with a within subject factor of variance (V_{UCM} and V_{ORT}) and a between subject factor of group (healthy individuals and stroke survivors). Independent t-tests were used to compare between group differences of ΔV and V_{TOT} and paired t-test were used to compare the differences between V_{UCM} and V_{ORT} within stroke and healthy population. Pearson's correlation was used to assess the relationship between FMA scores and V_{TOT} in stroke survivors. Point biserial correlation was used to assess the relationship between the number of muscle modes and FMA scores of stroke survivors. The significance level was set at $p<0.05$. All statistics were performed in SPSS version 21 (IBM Co., Somers, NY).

The difference between the two variance components (V_{UCM} and V_{ORT}) were not significantly different between healthy individuals and stroke survivors ($p=0.08$). However, V_{UCM} was significantly greater than V_{ORT} in stroke survivors ($p=0.001$; $V_{UCM}=0.0077\pm0.0037$; $V_{ORT}=0.0035\pm0.0023$) and healthy individuals ($p=0.001$; $V_{UCM}=0.0039\pm0.0014$; $V_{ORT}=0.0012\pm0.0005$) (Figure. 2.1) suggesting the individuals' ability to stabilize footpath during the swing phase of walking.

The total variance was significantly greater for stroke survivors ($p=0.001$; Healthy=0.0031 ± 0.0009; Stroke=0.0062 ± 0.0031) in comparison to the healthy individuals (Figure. 2.2). No significant differences were seen in the relative variance difference between stroke survivors and their healthy age and gender matched controls (p=0.37; Healthy=0.5±0.17; Stroke=0.38±0.24) (Figure. 2.3). There is no significant correlation between FMA and V_{TOT} (r= -0.376, p=0.22) and between FMA and the number of muscle modes (r= 0.529, p=0.077). Two out of twelve stroke survivors required three muscle modes to explain VAF > 90% for all muscles. However, the remaining ten stroke survivors and all the healthy individuals required four modes to explain VAF > 90%.

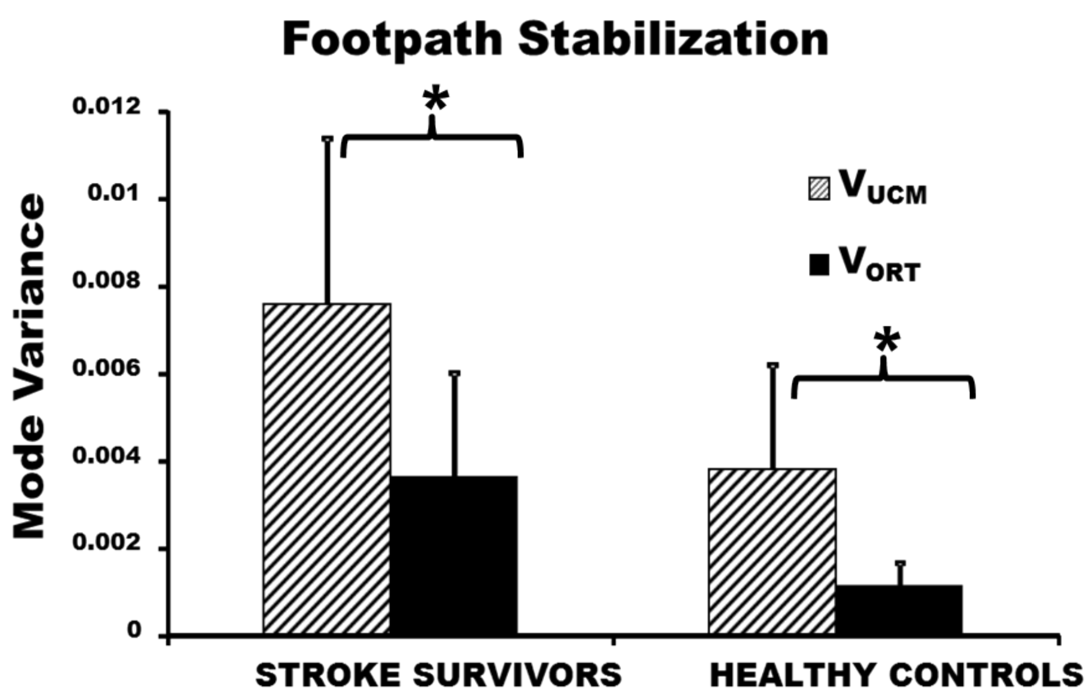

Figure 2.1 Variance components averaged across swing phase of walking. The hatched bars represent mode variance that leads to a stable footpath (V_{UCM}) averaged across stroke subjects (left), healthy subjects (right). The solid bars represent mode variance resulting in an inconsistent footpath averaged across stroke (left) and healthy (right) subjects. Error bars represent the standard deviation across subjects. * p<0.05.

2.5 Discussion

All the subjects demonstrated an ability to stabilize the footpath during the swing phase of walking. However, the ability to stabilize the footpath was not significantly different between the groups. The stoke survivors had a greater total variance (V_{TOT}) than the age and gender matched healthy controls. Furthermore, individuals with lower impairment level following stroke showed a possible trend towards larger number of muscle modes (p=0.077) suggesting greater ability to activate more muscle modes independently.

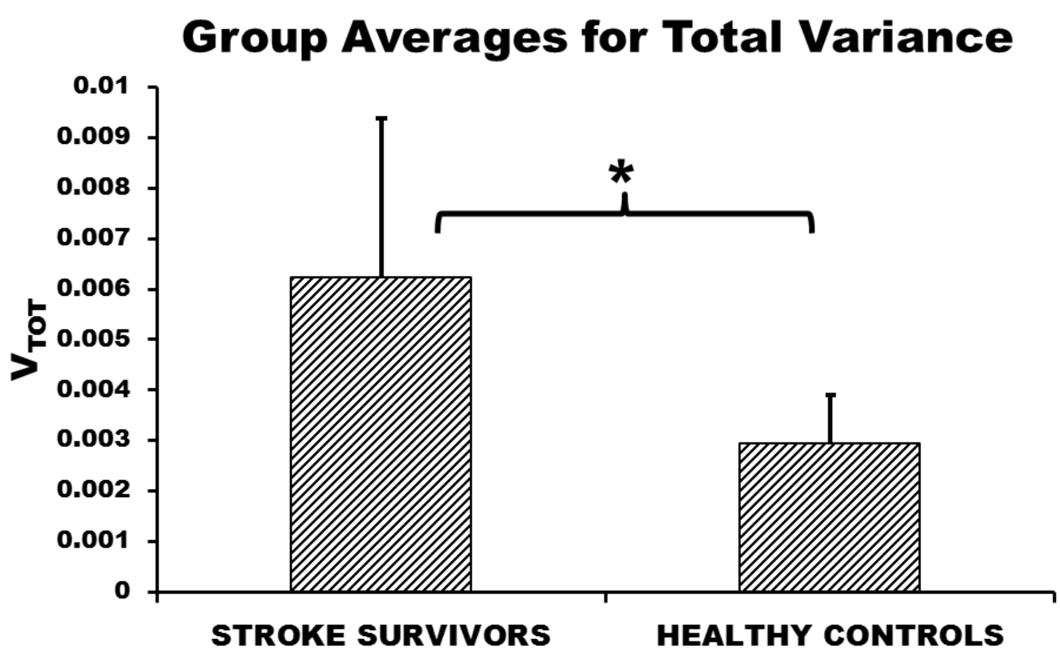

Figure 2.2 Total variance during the swing phase of walking averaged across stroke subjects and healthy matched controls. Error bars represent the standard deviation across subjects. * p<0.05.

The data indicates a positive relationship between the number of muscle modes and the Fugl-Meyer assessment score for each subject, but the correlation is not significant (Figure. 2.4). These results agree with previous literature suggesting that individuals may have difficulty in independently controlling the muscle modes following stroke [56].

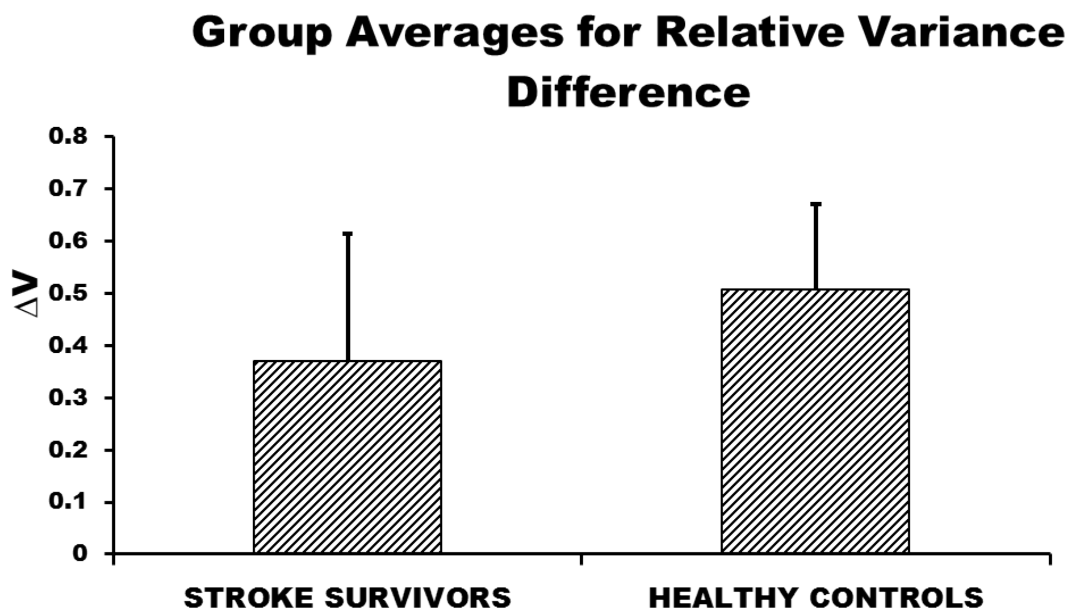

Figure 2.3 Averaged (across subjects) relative variance difference (ΔV) during the swing phase of walking. Error bars represent the standard deviation across subjects.

2.5.1 Stroke Survivors and Healthy People Demonstrated the Ability to Stabilize the Footpath During Swing Phase

The results in the current study show that V_{UCM} was significantly larger than the V_{ORT} in healthy individuals. This suggests that footpath is an important task variable during swing phase and the CNS uses the abundant DOF at the level of muscle modes to stabilize the vertical and AP position of the foot during walking. Furthermore, individuals were able to retain the ability to stabilize the footpath following stroke. The ability of the CNS to use motor abundance to stabilize a task variable in healthy individuals is consistent with previous literature [64, 87, 111].

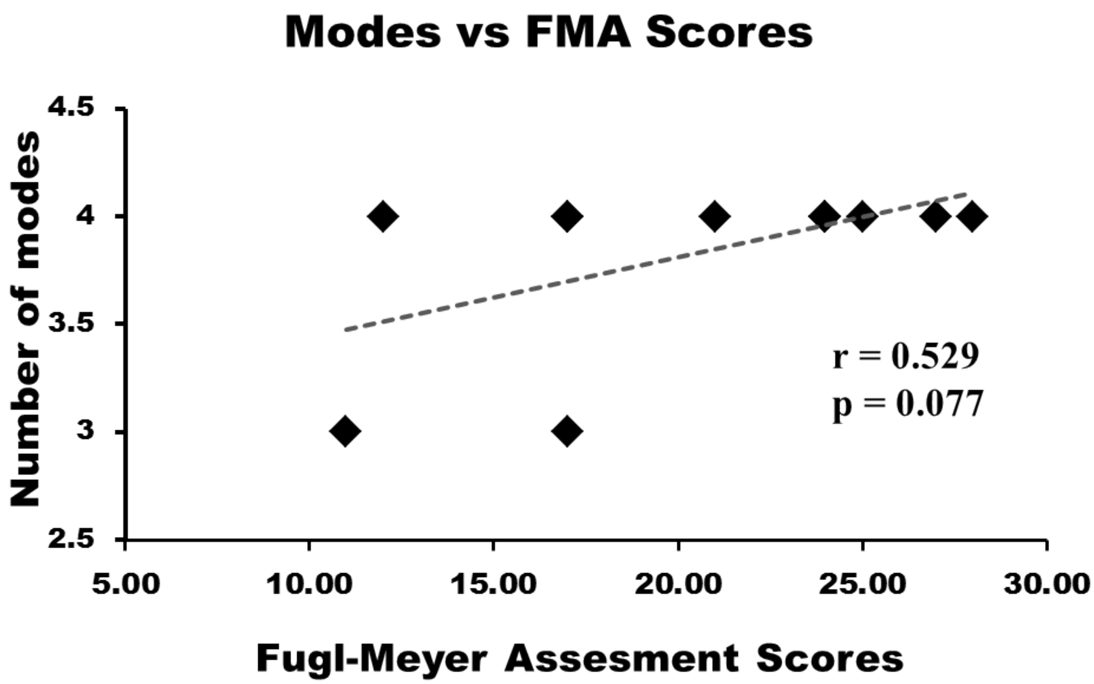

Figure 2.4 Correlation between the number of muscle modes and stroke survivors' FMA scores. Each data point represents individual subject's data.

Studies involving various activities such as anticipatory postural adjustments, walking, stepping, and pointing have demonstrated that multiple DOF at the level of joints or muscles covary across trials to stabilize a task variable important for successful accomplishment of a task [63, 87, 114, 115]. Furthermore, it has been shown previously that individuals retain the ability to use the motor abundance for stabilizing a task variable to a certain extent even after a neurological injury [116, 117]. Therefore, the results in the current study are consistent with previous literature [116] demonstrating the ability of stroke survivors to stabilize the footpath.

2.5.2 Stroke Survivors had Greater Variance Compared to Healthy Controls

The stroke survivors had a larger V_{TOT} in comparison to the healthy individuals, therefore agreeing with our second hypothesis. Balasubramanian et.al [107] have shown that the variability of gait parameters in stroke survivors' paretic limb is greater than the non-paretic limb and healthy individuals. In addition, previous reaching studies have shown an increase in the trial-to-trial variability of hand path movement and movement timing to reach a target following stroke in comparison to healthy people [116, 118]. Therefore, the results from the current study are consistent with previous literature suggesting that stroke survivors are more variable in comparison to healthy individuals. A recent study has shown that a more challenging reaching task may result in an increase in the total joint variance used to stabilize a task variable [119]. Due to the neuromuscular impairments following stroke, walking may be more challenging for stroke survivors in comparison to healthy individuals [120]. Therefore, it is possible that the stroke survivors may use a larger variance to stabilize the footpath across cycles in comparison to healthy control subjects.

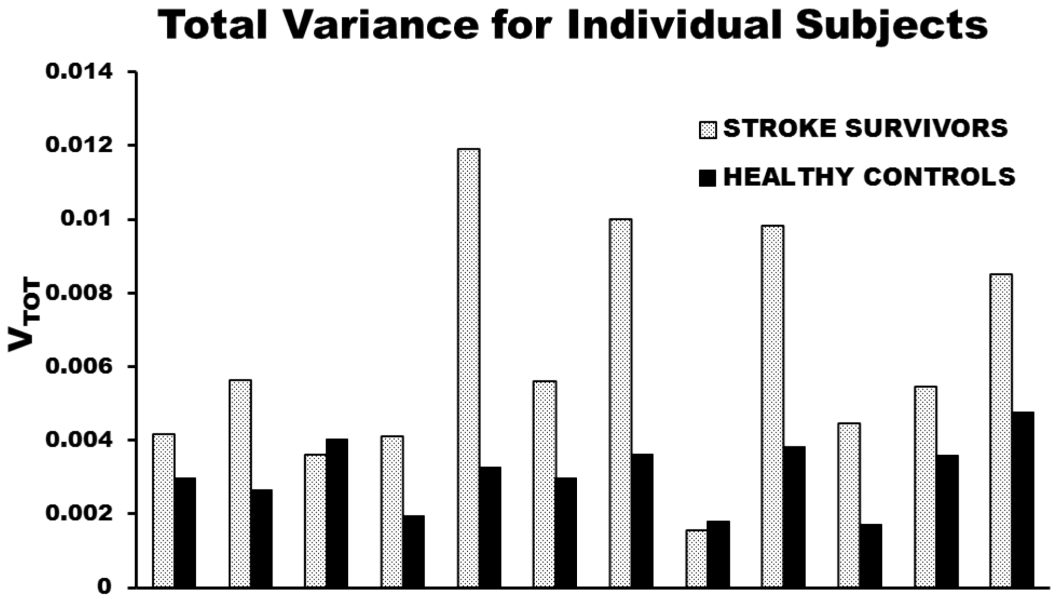

Figure 2.5 Total variance (V_{TOT}) averaged across swing phase of walking for each subject. The grey solid bars represent the V_{TOT} of each stroke survivor and black solid bars represent the V_{TOT} of corresponding healthy control subject.

However, S3 and S8 have smaller amount of V_{TOT} in comparison to their age and gender matched controls (Figure. 2.5). These two subjects also have a lower ΔV compared to other stroke survivors. The smaller ΔV suggests that a large part of muscle mode variability leads to an unstable footpath. Therefore, these two individuals may be at a greater risk of tripping and falling, and may have reduced V_{TOT} as a compensatory strategy to minimize the risks of falls.

2.5.3 No Significant Differences Were Seen Between the Healthy and Stroke Population in Their Ability to Stabilize the Footpath

We had expected that the relative variance difference (ΔV) during walking would be greater in the healthy individuals in comparison to the stroke subjects. This would mean that the healthy subjects have a more stable footpath across cycles. The results from the current study show a trend of higher ΔV in healthy population compared to the stroke survivors. However, there was no significant difference in the ΔV between the groups. These results agree with a previous reaching study where no significant differences were observed in the ability to stabilize the task variable between stroke survivors and healthy age matched controls [116].

Previous studies on reaching and standing posture with healthy individuals [111, 121] have reported a higher ΔV which is closer to one compared to healthy people in the current study. This would mean that the ability to stabilize a task variable in the current study is lower than the previously reported values. However, a recent study looking at ML footpath stabilization during walking has reported similar values of ΔV as the current study [87]. As suggested by Krishnan et al [87], it is possible that the CNS does not control the footpath during walking as precisely as task variables during reaching or standing posture. Healthy individuals try to optimize their walking pattern by decreasing the variance and minimizing energy expenditure [122], which may explain the smaller ΔV for footpath stabilization.

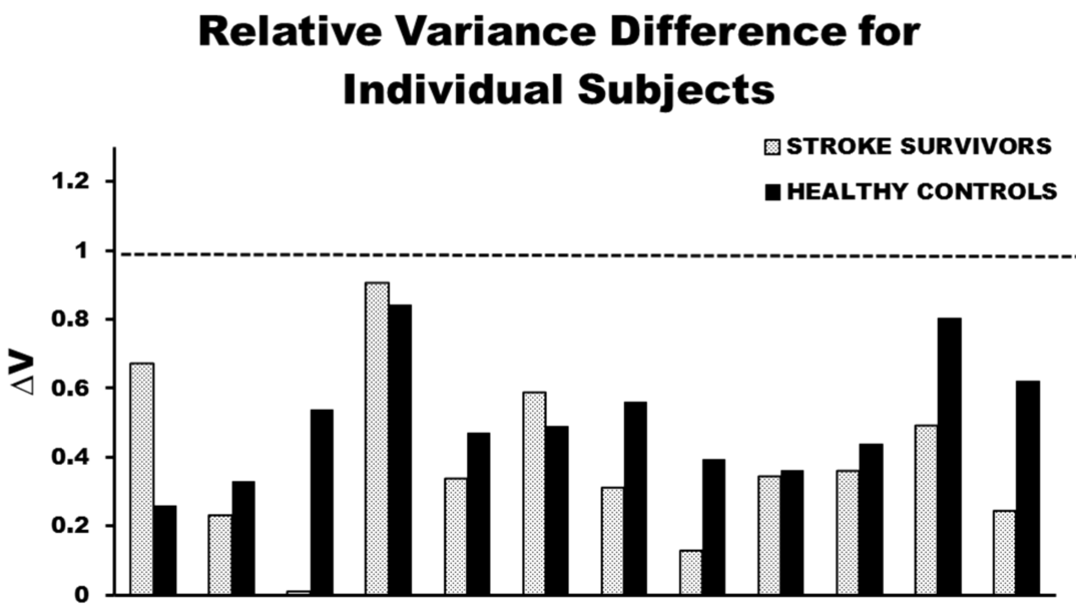

Figure 2.6 Relative variance difference (ΔV) averaged across swing phase of walking for each subject. The grey solid bars represent the ΔV of each stroke survivor and black solid bars represent the ΔV of the corresponding healthy control subject. The horizontal line represents the value one (ΔV with a value close to positive one suggests greater ability of an individual to stabilize the footpath).

Most of the healthy individuals had higher ΔV compared to the stroke survivors. However, individual differences with a higher ΔV in stroke survivors compared to their age and gender matched controls were observed in S1, S4, and S6 (Figure. 2.6). These stroke survivors may be using a different strategy than healthy people to stabilize their footpath. Previous studies have shown that the stroke survivors have lower foot clearance and greater step-to-step variability, and therefore have greater risks of falls during walking [10, 83]. Consequently, some stroke subjects may partition more of the total variance in stabilizing the task variable by increasing their V_{UCM} to compensate for gait instability.

One limitation of the current study is that we have not looked at the other task variables that can be important for maintaining stability during walking, such as center of mass position. Further studies are needed to understand the control of these task variables and whether the CNS tries to prioritize the stabilization of a variable based on the different phases of gait. It is also important to understand the differences between the paretic and the non-paretic limb of stroke survivors in addition to the differences between stroke subjects and healthy individuals. The results from the current study may help us gain a better understanding of the relationship between muscle activation during walking and footpath control post-stroke. However, it is possible that the muscle activation and joint movements of the contralateral limb may play some role in altering the footpath during swing. Therefore, further investigations are needed with the inclusion of muscles of the stance limb in the analysis to completely understand the footpath control during walking.

In the current study trends between the functional impairment levels of the stroke survivors and total variance as well as the number of modes has been observed. However, future studies with greater number of subjects and more diverse levels of motor impairments post-stroke may be required to understand the relation between impairment levels and the ability to stabilize the footpath.

2.6 Conclusion

The results from the current study suggest that the CNS uses motor abundance to stabilize the vertical and AP footpath during the swing phase of walking in healthy people. Furthermore, this trend is retained in individuals following stroke. Therefore, footpath is an important task variable that is controlled by the CNS during walking. The stroke population has greater total variance compared to the healthy people suggesting that the stroke survivors are more variable. However, the relative variance difference is not significantly different between the two populations. Thus, it is possible that people post-stroke achieve a similar ability to stabilize the footpath compared to healthy individuals.

Chapter 3

ASSIST-AS-NEEDED ROBOT-AIDED GAIT TRAINING IMPROVES WALKING FUNCTION IN INDIVIDUALS FOLLOWING STROKE

3.1 Abstract

A novel robot-aided assist-as-needed gait training paradigm has been developed recently. This paradigm encourages subjects' active participation during training. Previous pilot studies demonstrated that assist-as-needed robot-aided gait training (RAGT) improves treadmill walking performance post-stroke. However, it is not known if there is an over-ground transfer of the training effects from RAGT on treadmill or long-term retention of the effects. The purpose of the current study was to examine the effects of assist-as-needed RAGT on over-ground walking pattern post-stroke. Nine stroke subjects received RAGT with visual feedback of each subject's instantaneous ankle malleolus position relative to a target template for fifteen 40-minute sessions. Clinical evaluations and gait analyses were performed before, immediately after and 6 months post-training. Stroke subjects demonstrated significant improvements and some long-term retention of the improvements in their self-selected over-ground walking speed, Dynamic Gait Index, Timed Up and Go, peak knee flexion angle during swing phase and total hip joint excursion over the whole gait cycle for their affected leg ($p<0.05$). These preliminary results demonstrate that subjects improved their over-ground walking pattern and some clinical gait measures post-training suggesting that assist-as-needed RAGT including visual feedback may be an effective approach to improve over-ground walking pattern post-stroke.

3.2 Introduction

Stroke is a leading cause of serious long-term disability in the elderly. Each year approximately 795,000 people experience a new or a recurrent stroke [3]. Lower-extremity sensorimotor impairment is frequently seen in people following stroke [4]. Stroke survivors usually have reduced joint excursion, insufficient forward propulsion, and hyperactive reflex responses, which leads to a slow, asymmetrical, and unstable walking pattern [9, 10, 12]. In addition, stroke survivors tend to use inefficient compensatory strategies for the gait deficits such as a leg circumduction or abnormal elevation of the pelvis to compensate for insufficient foot clearance during swing. Overall, these altered walking patterns lead to high energy expenditure [13] and may further reduce their social participation and independence in activities of daily living [5].

Body weight supported treadmill training (BWSTT) is one of the approaches for gait retraining post-stroke [20, 21]. An advantage of BWSTT is that partial body weight support makes it easier for patients to control their lower limbs and trunk during training. BWSTT has shown significant therapeutic effects in improving patients' gait speed, walking endurance, and functional walking capacity [20, 21, 24]. However, the major drawback of this training is that it is labor-intensive, requiring one or two therapists to manually assist patients' leg motion and stabilize their trunk. In addition, the manual assistance provided during the training varies from one therapist to another and thus, the training may not be performed in a consistent manner [123]. Duncan et al (2011) suggests that BWSTT is not superior to a home-exercise program in promoting functional gait recovery. Thus, clear evidence for the effectiveness of BWSTT in the post-stroke population is still lacking [27].

Robotic lower-limb exoskeletons have been developed to overcome some of the aforementioned limitations of BWSTT. Robot-aided gait training (RAGT) with continuous assistance tends to move the patient's leg passively through a prescribed target path, and has been shown to be less effective than conventional therapy [124]. This may be because the subjects' physical effort is substantially reduced due to the continuous assistance. A novel complaint force field for RAGT was developed to provide assistance when needed, as an alternative to continuous assistance [31, 33]. Previous studies showed that both neurologically impaired and intact individuals increased their active participation by showing greater heart rate, muscle activation, and physical exertion during training when using an assist-as-needed paradigm [36, 37, 48]. In addition, a recent case study compared the two training strategies, assist-as-needed and continuous assistance paradigms, on a single stroke survivor [42]. Their preliminary results suggest that the assist-as-needed paradigm is more effective than the continuous assistance paradigm, showing more improvements in clinical measures and walking speed. The compliant force field used during the assist-as-needed paradigm preserves a basic feature of walking, that is, the presence of step-to-step variability [34]. It is possible that the movement variability encourages more active participation from the subjects, and leads to better gait recovery [125]. However, there is still limited evidence supporting the effectiveness of the assist-as-needed RAGT on individuals post-stroke. Furthermore, it has been suggested that restricting degrees of freedom of the trunk as a result of walking with the robotic exoskeleton may limit improvements in subjects' gait pattern [32]. An **A**ctive **L**eg **EX**oskeleton (ALEX) developed in our laboratory provides additional degrees of freedom for trunk and hip movement in comparison to the commercially available Lokomat [126]. This can be an advantage over the widely used Lokomat and may allow a more natural gait pattern.

The purpose of the current study was to investigate the effectiveness of assist-as-needed RAGT with ALEX on the walking capacity of individuals post-stroke. A previous pilot study from our lab demonstrated that two stroke survivors improved their treadmill walking patterns after 15 sessions of assist-as-needed RAGT that included visual feedback of their instantaneous and target ankle malleolus position [31]. In addition, a recent pilot study from Krishnan et al. showed that a single stroke survivor had substantially improved muscle coordination, propulsive ground reaction forces, and malleolus path after receiving the assist-as-needed RAGT [44]. Although those results are promising, the conclusions were based on the data from only one or two stroke survivors. Moreover, no information regarding long-term retention of the training effects from the assist-as-needed paradigm is available in the previous studies. In the current study, we investigated whether the RAGT using an assist-as-needed paradigm would facilitate changes in the walking patterns and functional capacity of individuals post-stroke and whether these changes would be retained 6 months following training. We also investigated if the training effects could be transferred to over-ground walking. We hypothesized that subjects would show improvements in their walking patterns and sensorimotor function following gait training, and these changes would be retained to some extent even 6 months after the training.

3.3 Methods

3.3.1 Subject Information

Nine stroke survivors (7 males, 2 females) who had sustained a stroke more than 3 months prior to the study gave written informed consent to participate in a study, approved by the University's Review Board. A summary of the stroke survivors' characteristics is listed in Table 3.1. A physical therapist screened all the subjects for the exclusion criteria. Subjects were excluded if they had evidence of multiple strokes, chronic white matter disease on MRI, congestive heart failure, peripheral artery disease with intermittent claudication, cancer, pulmonary or renal failure, unstable angina, uncontrolled hypertension (> 190/110 mmHg), dementia (Mini-Mental State exam < 22) [113], severe aphasia, orthopedic conditions affecting the legs or the back, or cerebellar signs (e.g., ataxia).

3.3.2 Device and Assist-as-needed Force Field Description

This study used ALEX developed at the University of Delaware (Figure. 3.1), details of which were described previously [31, 127]. ALEX was used to apply an assist-as-needed compliant guidance force on the affected leg of the subjects during training. Each subject was provided with visual feedback of the instantaneous malleolus position and a target template based on the spatial location of the lateral malleolus. The target template for the training was based on the normalized walking pattern of ten healthy elderly individuals that were recorded previously at 17 different speeds from 0.6 to 2.2 mph. Templates for the malleolus path were adjusted to each stroke survivor's leg length at a given speed. The malleolus path of healthy individuals was considered to be 100%, and the stroke survivors' baseline pattern was considered as 0%.

Table 3.1. Demographic Detail of the Stroke Survivors.

Subject ID	AGE (yrs)	Duration Post-stroke (months)	Side affected	Gender
S1	72	41	R	M
S2	47	38	R	M
S3	78	29	R	M
S4	56	95	L	M
S5	80	53	L	M
S6	60	3	R	F
S7	43	3	R	M
S8	67	20	L	M
S9	70	149	L	F

The stroke survivors' malleolus path was scaled at each data point to a certain percentage of the healthy data to generate the target template [31]. Scaling of the stroke survivor's path was increased towards that of the healthy template across training sessions. A compliant force field with an assist-as-needed paradigm provided guidance in the form of a virtual (elastic) tunnel around the target template that works similar to an elastic band, tending to bring the subject's ankle towards the target path. The force field included normal and tangential forces. The normal force was applied when the subject's instantaneous malleolus position went beyond the virtual tunnel surrounding the target template. The amount of normal force was proportional to the square of the deviation between subject's instantaneous malleolus position and the tunnel around the desired target path. A minimal tangential force helped the subjects to move along the target malleolus path (Figure. 3.2). Computation of the amount of F_N required was based on equation (10).

$$F_N = K_N \left(\frac{/\, d \,/ - D_0}{D_N} \right)^2 \qquad (10)$$

Here K_N or stiffness is a constant with force units, d is the distance between the subject's instantaneous malleolus position and the desired position on the target path, D_0 is the width of virtual tunnel, and D_N is a constant with length units [31].

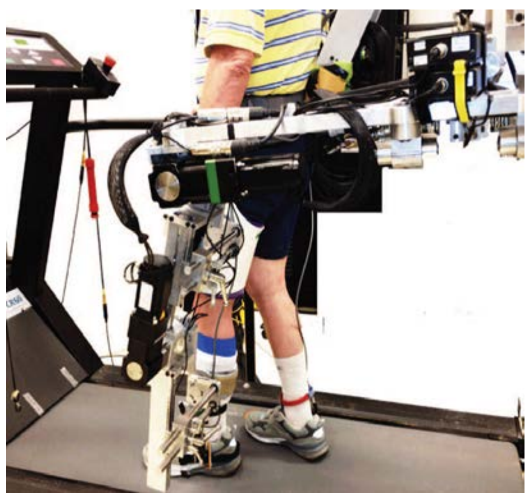

Figure 3.1 The active leg exoskeleton (ALEX) worn by the subjects on their affected extremity during training and treadmill evaluation.

3.3.3 Training and Evaluation Protocol

Subjects received a total of 15 training sessions by having 5 daily sessions per week, every other week for 3 weeks. Each training session included eight 5-minute training bouts with rest breaks after every bout. Subjects received visual feedback on their instantaneous malleolus position and the target template as well as functional electrical stimulation (FES) of their ankle plantarflexors and dorsiflexors during alternating minutes. Pulse duration for dorsiflexors was set with subjects seated, to achieve a neutral ankle joint position (0°) with minimal ankle eversion or inversion. For plantarflexors the subjects stood in a position similar to terminal double support of the paretic leg. Pulse duration was set to achieve lifting of the paretic heel off the ground or until the subject's maximal tolerance was reached, whichever occurred first.

Table 3.2 Participants' Characteristics at Baseline.

Timed Up and Go (s)	**Dynamic Gait Index**	**Fugl-Meyer Assessment**	**Six-Minute Walk Test**	**Self-Selected Speed (m/s)**
14.47	13	NA	NA	0.51
9.66	20	NA	474	1.06
18.62	13	19	311	0.74
7.6	16	24	476	1.04
15.6	12	25	268	0.75
29.3	9	11	72	0.15
16.2	12	21	232	0.53
29.3	8	12	150	0.29
13.2	15	28	332	0.78

The stimulation intensity was set using 300-ms long, 30-Hz train with 150-Volt amplitude. The FES stimulation pattern comprised a high-frequency (200-Hz) 3-pulse burst followed by a lower frequency (30-Hz) constant frequency train. However, FES was provided to S1 only for the third week of training, and S2 only for the plantarflexors for the entire period of training.

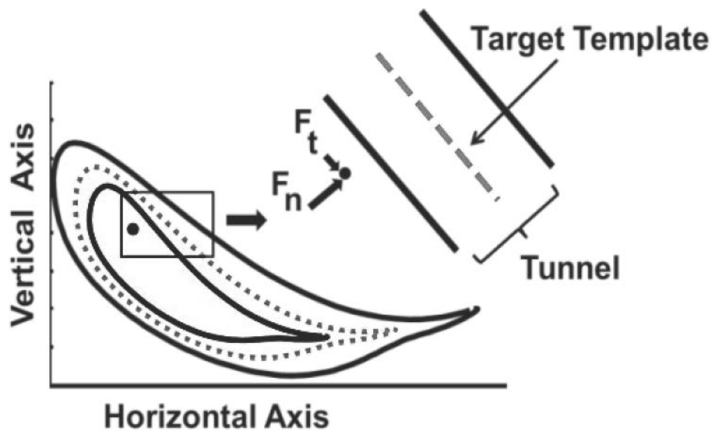

Figure 3.2 Target template based on ankle malleolus and application of the compliant force field. The dashed line represents the target template based on the malleolus path and the black solid lines represent the walls of the virtual tunnel on either sides of the template. The solid black dot represents instantaneous malleolus position of the subject with the normal (Fn) and tangential (Ft) forces represented by the solid black arrows moving the subject's ankle closer to the template.

The force field was applied continuously for entire training bout. The size of the target was not changed within a single session; however, the assistance was decreased gradually over the training bouts, allowing the subjects to control their malleolus position more independently. Two levels of stiffness and two sizes of the virtual tunnel were used. A high (HS = 0.760 N) and a low (LS = 0.125 N) stiffness coefficients (KN) as well as a narrow width (NW = 1cm) and a larger width (LW = 2cm) of the virtual tunnel. The robotic assistance across training bouts was reduced by decreasing the stiffness and/or increasing the width of the virtual tunnel around the target template [31]. The training speeds and the size of the target template were increased gradually with the progression of the training, based on the subject's performance on the previous training session.

All subjects underwent gait analyses of the paretic leg on the treadmill using ALEX and during over-ground walking using eight-camera motion capture system, as well as a clinical examination before training (baseline), immediately after training (post-training), and 6 months after training (follow-up). Each clinical evaluation session included lower-extremity Fugl-Meyer Assessment (FMA) [128], Dynamic Gait Index (DGI) [129], Six-Minute Walk Test (6MWT) [130], and Timed Up and Go test (TUG) [131] (Table 3.2). The walking evaluation on the treadmill with ALEX was performed without the force field guidance and visual feedback at subjects' baseline treadmill walking speeds. For the gait evaluation during over-ground walking, subjects were evaluated at their self-selected speed.

3.3.4 Data Acquisition and Analysis

Lower-limb joint angles and foot pressure sensor data were collected when walking with ALEX on the treadmill. Interlink Electronics FSR 406 pressure sensors placed on the sole of the shoes were used to define the gait events of each leg. The area between the target and the actual malleolus path during the swing phase was computed to measure the effects of training on learning of the normalized target path [31]. If subject's actual malleolus path matches the prescribed malleolus path more closely post-training, the area between the actual and the target paths would be smaller than the area computed at baseline. A smaller area after training would indicate a pattern closer to healthy individuals.

During over-ground walking, lower-body kinematic data sampled at 120 Hz were collected by using an eight-camera motion capture system. For the first three subjects, a VICON (Oxford, UK) motion capture system was used. Kinematic data for the remaining individuals was captured using an eight-camera Qualisys (Gothenburg, Sweden) motion capture system because of a switch in labs. Visual 3D (C-Motion Inc., Rockville, MD) was used to compute hip, knee and ankle joint angles. Peak flexion angles during swing phase of gait cycle were computed for further analysis.

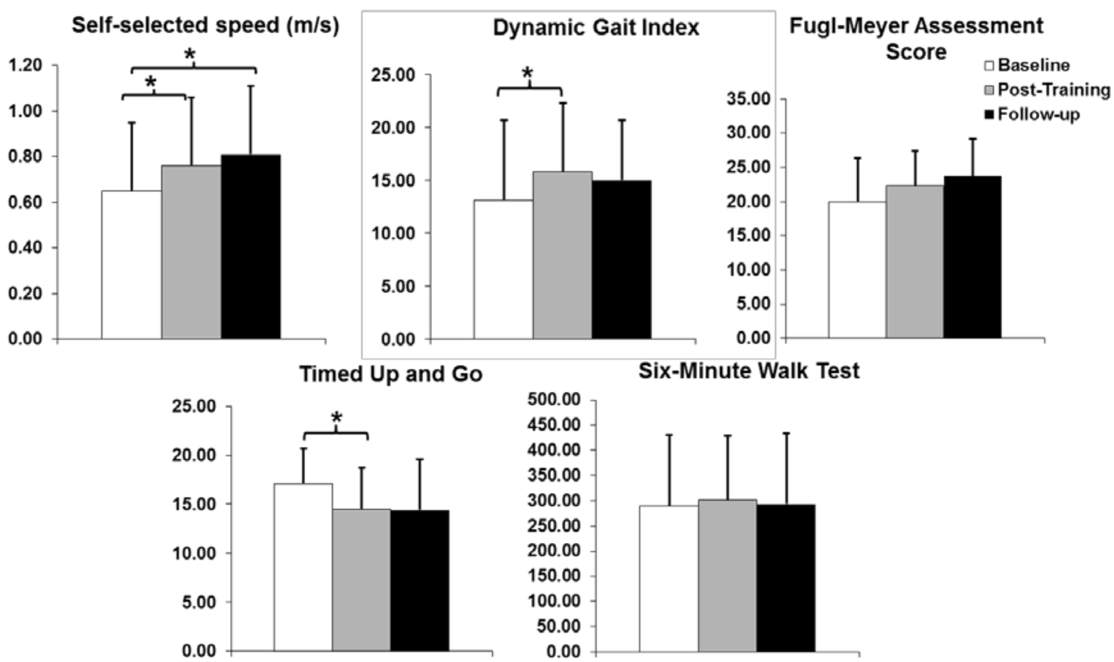

Figure 3.3 Clinical outcome measures averaged across subjects at baseline, after training (post-training), and 6 months after training (follow-up). Error bars represent the standard deviation across subjects. * p<0.017

3.3.5 Statistical Analysis

Due to the small sample size, we used the non-parametric Friedman's test to test for differences in the gait parameters and clinical outcome measures among the three evaluation sessions (i.e., baseline, post-training, 6-month follow-up). The significance level was set at $p<0.05$. If the main effect was significant, we used Wilcoxon signed rank test to compare each pair of the evaluation sessions with adjusted $p<0.017$. All statistics were performed in SPSS version 20 (IBM Co., Somers, NY).

3.4 Results

3.4.1 Clinical Measures

Stroke survivors exhibited significant changes in their self-selected over-ground walking speed (Friedman's test, $p<0.01$), DGI ($p<0.01$), and TUG ($p<0.05$) after receiving training as compared to the baseline (Figure.3.3). For the self-selected walking speed, subjects showed significant improvements after the training that were retained 6-months post- training (Wilcoxon signed rank tests, $p<0.017$). DGI and TUG scores of the subjects improved significantly after training (Wilcoxon signed rank test, $p<0.017$) but the changes were not retained 6-months post-training. The FMA test was not performed for the first two subjects, and there was a significant main effect. There were no statistically significant difference in the FMA scores after training or at the 6-month follow-up (Wilcoxon signed rank tests, $p>0.017$) (Figure.3.3). The 6MWT was not performed on the first subject. There were no statistically significant differences in the 6MWT among the evaluation sessions (Friedman's test, $p=0.3$) (Figure.3.3).

3.4.2 Over-ground Kinematic Data

Subjects showed significant changes in peak knee flexion during the swing phase (Friedman's test, $p<0.05$ after training (Wilcoxon signed rank test, $p<0.017$), but the increase was not retained at the 6-month follow-up (Figure.3.4).

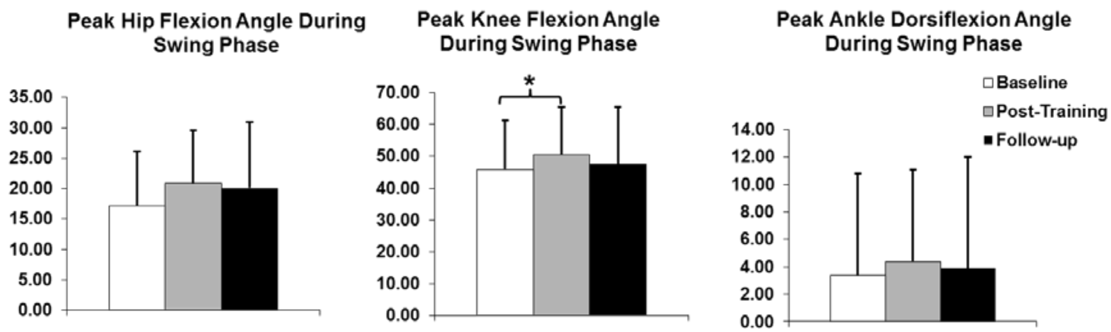

Figure 3.4 Peak hip and knee flexion angles and peak ankle dorsiflexion angle (°) during the swing phase of gait cycle averaged across subjects for the paretic leg. Error bars represent the standard deviation across subjects. * $p<0.017$.

3.4.3 Ankle Lateral Malleolus Path Area

There were no significant differences in the area between subjects' malleolus path and the target path derived from the healthy subjects recorded previously (Friedman's test, $p>0.05$). However, five out of the nine subjects demonstrated a smaller area following training. This indicates that these stroke survivors walked with their malleolus paths closer to the target path even without the visual display. On the contrary, three subjects showed an increase in the area. This increase resulted from an exaggerated high stepping pattern while walking in the robotic exoskeleton without the compliant force field. The single remaining subject did not show changes following training in the area relative to the target path (Figure. 3.5).

3.5 Discussion

There were significant improvements in walking speed, some of the over-ground kinematic measures, and some of the clinical measures after training. The improvement in walking speed was retained 6 months after training. However, little change was seen in the ankle path area following training. Therefore, the current findings partially support our hypothesis that assist-as-needed RAGT would improve walking patterns and functional capacity post-stroke.

Current literature lacks information regarding changes in over-ground kinematics of the paretic leg following RAGT. This information is critical because the ultimate goal of rehabilitation is to transfer the training effects to over-ground walking. Our results showed that stroke survivors improved joint kinematics during over-ground walking, such as significant increases in the peak knee flexion angle during the swing phase. However, there were no significant improvements in the ankle joint angles, suggesting limited training effects of FES of ankle plantarflexors and dorsiflexors. Further investigation is required to determine whether the improvements in the walking pattern post-training were due to the effects of the compliant force field, or FES, or a combination of both. In addition, five out of the nine stroke survivors walked with smaller area following training suggesting a malleolus path that was closer to the target template post-training. Three subjects demonstrated an increase in their malleolus path area post-training. This increase in the area was due to a higher stepping during treadmill walking post-training and suggests greater compensations for foot clearance used by these subjects.

There have been a limited number of studies investigating the effectiveness of RAGT post-stroke. Previous studies compared the effects of RAGT with BWSTT or conventional physical therapy [32, 124, 132]. However, there is still a lack of strong evidence supporting the effectiveness of any gait training intervention on the functional recovery post-stroke [20, 21, 27, 32, 124]. In these previous studies, the RAGT employed a control algorithm that provided continuous assistance to the subjects regardless of their online performance [32]. Conversely, a compliant force field as tested in the current study allows variability of stepping movements and requires greater active participation from the subjects. It is likely that the compliant force field can result in larger improvements of functional walking ability than the continuous assistance that forces the limb through a fixed movement path because, in the latter case, participants rely on the robotic assistance and reduce their effort [35, 42, 44].

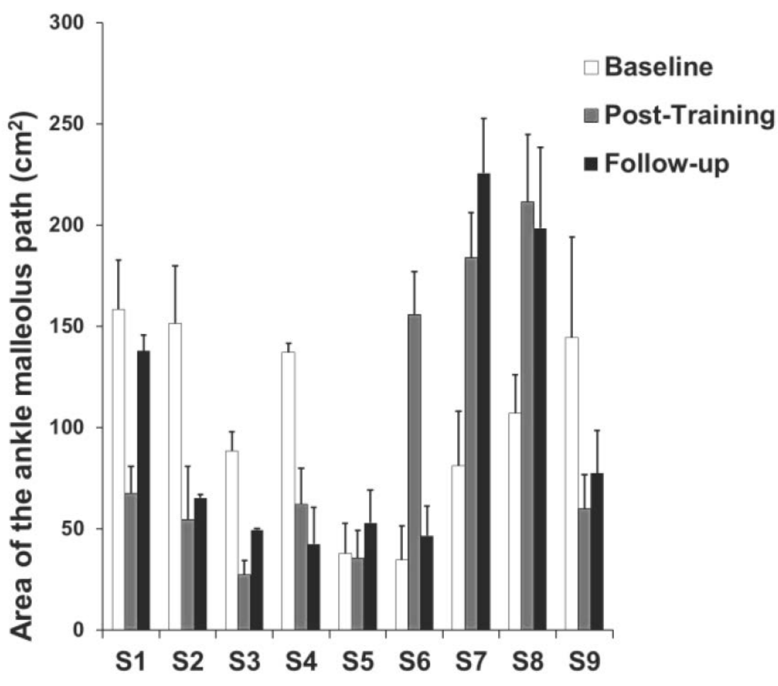

Figure 3.5 Each subject's area between the ankle malleolus path at their self-selected walking speed and the target template averaged across swing phase. Error bars represent standard deviation across gait cycles.

Further investigation is needed to determine whether assist-as-needed RAGT is superior to training with continuous assistance or BWSTT. Although the assist-as-needed paradigm theoretically provides advantages over continuous assistance, the changes in gait in the current study e.g., self-selected walking speed (0.65±0.3 to 0.76±0.3 m/s) and the 6 MWT (289.4±142.2 to 301.7±128.1 meters) were similar to changes in these parameters (self-selected speed:0.45±0.19 to 0.52±0.21 m/s; 6MWT:170±86 to 186±88 meters) in previous studies that employed a Lokomat to provide continuous assistance [32, 124]. In addition, larger improvements have been reported after BWSTT (self-selected walking speed:0.43±0.22 to 0.56±0.28 m/s; 6MWT:170±86 meters to 204±96 meters). However, subjects' baseline walking speeds and endurance in the current study were generally higher than the subjects in Hornby et al [32], and it is possible that some of our subjects may have shown a ceiling effect. A recent study in our lab with healthy individuals suggests that an error-augmentation training paradigm, where the robotic force field exaggerates the subjects' error in matching the target can result in better short-term learning effects than the assist-as-needed paradigm [133]. Therefore, it may be possible that stroke survivors with higher functional walking ability may benefit from a more challenging training protocol such as an error augmentation paradigm.

The current study provided intermittent visual feedback of the instantaneous ankle malleolus positions and target template to the subjects as compared to the previous studies where feedback was based on hip or knee joint information [33]. Recent studies have suggested that the central nervous system controls important variables for task success [109], for example center of pressure to maintain standing posture using multiple degrees of freedom of the joints or muscles [63]. It has been suggested that the foot trajectory during the swing phase may be an important variable that is controlled to prevent falls during walking [80, 110]. In addition, to regain walking ability, it has been shown that people with neurological disorders might benefit more from task-based training that encourages developing new muscle activity pattern for task success instead of a training that imposes reconstruction of normal muscle activity pattern [134]. Thus, it might be more effective to provide feedback on the performance of a critical task-relevant variable (e.g., malleolus position) than feedback on the performance of an individual joint (e.g., hip).

A major limitation of the current experiment is the limited sample size. The conclusions of this study were based upon data from nine stroke survivors. Additionally, in the current study, most of the subjects had mild to moderate impairment based on Perry's [135] classification. Long-term training with stroke survivors with more diverse levels of motor impairments may better determine which levels of subjects will benefit most from the assist-as-needed RAGT.

3.6 Conclusion

This study suggests that RAGT including a compliant force field with an assist-as-needed paradigm and visual feedback of malleolus path is a potential alternative for gait rehabilitation in people post-stroke. Subjects demonstrated improvements in their walking pattern on the treadmill. The effects of training were also modestly transferred to over-ground walking with changes in the functional walking ability, sensorimotor function, and walking speed.

Chapter 4

ROBOT-AIDED ASSIST-AS-NEEDED GAIT TRAINING VS BODY WEIGHT SUPPORTED TREADMILL TRAINING POST-STROKE

4.1 Abstract

Gait rehabilitation post-stroke is important as it leads to a more efficient walking pattern, improvement in social participation, and independence in the activities of daily living. Body Weight Supported Treadmill Training (BWSTT) is one of the often used paradigms for gait rehabilitation post-stroke. However, this training method is labor intensive and requires one or more therapist for manual assistance. To help address the limitations of BWSTT, robot-aided gait rehabilitation has been developed. Recently performance based robot-aided gait training (RAGT) by the application of a compliant force field with an assist-as-needed paradigm was suggested to be more beneficial than the robotic-training with continuous assistance post-stroke. The purpose of the current study was to compare the effects of BWSTT with assist-as-needed RAGT on the improvements in functional walking ability post-stroke. Twelve stroke survivors were randomly assigned to either BWSTT group or RAGT group. Clinical evaluations and gait analyses were performed before and immediately after the gait training for fifteen 40-minute sessions. Kinematic and electromyographic (EMG) data of the paretic leg were collected during over-ground walking at the subject's self-selected speed and peak flexion angles of the hip, knee, and ankle during swing phase were computed. Non-negative matrix factorization was used to identify the set of co-exciting muscles or modes from the EMG data.

Additionally, an uncontrolled manifold (UCM) approach was used to understand the role of muscle modes in stabilizing the footpath during the swing phase of walking. Stroke survivors demonstrated significant improvements in their self-selected over-ground walking speed, Functional Gait Assessment, Timed Up and Go, and peak knee flexion angle during swing phase following RAGT. Subjects receiving BWSTT demonstrated improvements in Six-minute walk test and the ability to stabilize the footpath. Furthermore, no significant differences between the groups were seen, but RAGT may be used as an alternative gait rehabilitation method as it requires less physical effort from the therapists compared to BWSTT.

4.2 Introduction

Stroke accounts for approximately 1 of every 19 deaths in the United States, and is a major cause of morbidity and mortality in the elderly population [3]. Furthermore, stroke imposes a significant burden on the healthcare expenditure of developed countries [136]. Thirty percent of stroke survivors have difficulty in walking without some assistance [3]. Gait deviations such as asymmetric gait, reduced walking speed, and compensatory strategies following stroke often lead to less efficient walking pattern [11]. Furthermore, balance and motor impairments post-stroke can result in diminished walking endurance [120]. Reduced functional walking ability post-stroke can limit the independence in the activities of daily living and result in a decline in social participation and quality of life [5]. Therefore, long-term disability following stroke poses a social and economic burden on the stroke survivors as well as the society.

Gait rehabilitation following stroke has the potential to improve walking economy and functional independence in activities of daily living [15]. Previous studies suggest that gait rehabilitation during walking provides better improvements than focusing on isolated components such as strength, balance, and coordination training [21, 137]. One such task specific gait rehabilitation strategy often used for stroke survivors is the body weight supported treadmill training (BWSTT). During BWSTT, an overhead suspension system and a harness are used to support the individuals' body weight partially and symmetrically. In addition, one or more therapists provide manual assistance to the individual to help in the movements of their paretic lower extremity and pelvis [20]. The BWSTT allows the individual to learn weight bearing and walking at faster speeds at an early stage post-stroke [138], therefore resulting in greater improvement of their walking capacity compared to conventional gait training methods [139, 140]. Some studies have shown improvements in walking speed, clinical measures, and walking endurance following BWSTT in comparison to conventional physical therapy treatment or gait training without body weight support in individuals with subacute or chronic stroke [20, 21, 138, 141]. However, this gait training strategy is labor intensive for the therapists [142]. Furthermore, a recent study has suggested that home exercises post-stroke are equally effective as BWSTT in improving functional walking ability [27].

Robot-aided gait training (RAGT) is less fatiguing for the physical therapists than BWSTT or conventional gait rehabilitation methods. However, previous studies have shown that RAGT results in similar or poorer improvements in the functional walking ability compared to BWSTT or conventional gait training post-stroke [32, 124]. RAGT provides continuous guidance to the subjects, while forcing them to follow a prescribed gait pattern. Previous literature has shown that the metabolic costs and muscle activation are significantly reduced with RAGT that provides continuous guidance in comparison to therapist assisted treadmill training [143]. Therefore, continuous assistance may result in decreased subjects' effort leading to smaller improvements in functional walking ability following gait training [42]. Furthermore, step-to-step variability is an important component of motor learning [39, 40] which is absent in fixed trajectory training. A performance based assist-as-needed RAGT was developed recently to address some of the aforementioned limitations of continuous assistance [31, 33]. A pilot study has demonstrated greater improvements in functional walking ability following an assist-as-needed gait training paradigm compared to continuous assistance [42]. In addition, a recent study has shown substantial improvements of muscle coordination, propulsive ground reaction forces, and ankle malleolus path during walking in a single stroke survivor following the assist-as-needed RAGT [44]. However, there is no previous literature comparing the effects of the compliant assist-as-needed paradigm with conventional physical therapy treatment or BWSTT.

Individuals following stroke may have impaired muscle and joint coordination [17, 18] which may affect their walking pattern [19]. Therefore, in addition to the clinical and kinematic measures it is important to understand the effects of gait rehabilitation strategies on motor coordination. Various measures have been used to understand the altered coordination and variability during walking in healthy individuals and people with neurological impairments [40, 122, 144]. However, these methods do not provide any information about the effects of the altered coordination on task specific variables such as fingertip position in a pointing task or foot position during walking. Impaired motor coordination can alter the control of task variables important for task success [116]. Therefore, understanding the effects of gait training on footpath control in addition to walking capacity can help us in understanding whether the impaired motor coordination can be improved following gait training. The purpose of the current study is to compare the effects of RAGT using an assist-as-needed paradigm and BWSTT on functional walking ability and footpath control post-stroke.

4.3 Methods

4.3.1 Subject Information

Twelve stroke survivors (9 males, 3 females) who had sustained a stroke more than 3 months prior to the study were recruited for the study (Table 4.1). Non-neurologically impaired gender matched control subjects were recruited whose age was within +/- 5 years of each stroke survivor's age. All subjects gave written informed consent to participate in the study, approved by the University's Review Board. Inclusion and exclusion criteria for stroke subjects and healthy controls are the same as described in the previous chapters.

Stroke survivors were quasi-randomly assigned to one of the two groups. The subjects recruited in the robot-aided gait training (RAGT) group were fitted to a robotically controlled exoskeleton that provided assistance to the swinging paretic limb during training while the subjects walked on a treadmill. Subjects in the control group receiving BWSTT received gait training with their body weight supported by a harness while two therapists provided manual assistance [142].

4.3.2 Robotic Device and Assist-as-needed Force Field Description

This study used an Active Leg Exoskeleton (ALEX) developed at the University of Delaware [127, 145]. ALEX was used to apply an assist-as-needed compliant guidance force on the subject's affected leg during training. Subjects were provided with visual feedback of a target template based on the position of the ankle lateral malleolus, and their instantaneous malleolus position. The target template for the training was based on the walking pattern of ten healthy individuals from previously recorded data, and the stroke survivor's leg length, as well as their baseline walking pattern. Malleolus path templates were generated specific to each walking speed. Healthy individuals' malleolus path was considered as 100% of the template, and the stroke survivors' baseline pattern was considered as 0%. The stroke survivor's malleolus path was scaled to different percentages of the healthy pattern to compute the target template for the training [31]. The assist-as-needed force field provides guidance in the form of a virtual (elastic) tunnel around the target ankle malleolus path that works similarly to an elastic band, tending to bring the subject's ankle towards the target path. The force field includes normal (F_N) and tangential forces (F_T) (Figure. 3.2). The normal force was applied when the subject's instantaneous ankle malleolus position went beyond the virtual tunnel surrounding the target malleolus path. Computation of the amount of F_N required was based on equation (10).

$$F_N = K_N \left(\frac{/ d / - D_0}{D_N} \right)^2 \tag{10}$$

Here K_N or stiffness is a constant with force units, d is the distance between the subject's instantaneous malleolus position and the desired position on the target path, D_0 is the width of virtual tunnel, and D_N is a constant with length units. A small tangential force (F_T) helps the subjects to move along the target malleolus path [31].

Table 4.1 Demographic Detail of the Stroke Survivors.

Training Group	Subject ID	AGE(yrs)	Duration Post-stroke (months)	Side affected	Gender	Fugl-Meyer Assessment
RAGT	S1	56	95	Left	M	24.00
RAGT	S2	80	53	Left	M	25.00
RAGT	S3	60	3	Right	F	11.00
RAGT	S4	43	3	Right	M	21.00
RAGT	S5	67	20	Left	M	12.00
RAGT	S6	70	149	Left	F	28.00
BWSTT	S7	58	17	Left	M	24.00
BWSTT	S8	48	11	Right	F	27.00
BWSTT	S9	75	14	Right	M	17.00
BWSTT	S10	54	12	Left	M	17.00
BWSTT	S11	59	35	Left	M	24.00
BWSTT	S12	59	3	Right	M	17.00

4.3.3 Training and Evaluation Protocol

Subjects in both groups received 5 daily training sessions per week, every other week, for three weeks. Each training session included eight 5-minute training bouts with rest breaks after every bout.

Robot-aided gait training group (RAGT): Subjects walked on the treadmill wearing the exoskeleton and received visual feedback on their instantaneous lateral malleolus position and the target lateral malleolus path, as well as functional electrical stimulation (FES) on their ankle plantarflexors and dorsiflexors during alternating minutes. Details of FES application have been discussed previously in chapter three. The assist-as-needed force field was applied continuously for the entire walking bout. The force field was decreased gradually within a single session by varying the stiffness and tunnel width, providing less constraint on the subject's swing phase movement. The target path was increased by a specified percentage of the normal path with the progression of the training based on the subject's performance on the previous day's training session.

Body Weight Supported Treadmill training group (BWSTT): Subjects walked on the treadmill with a specified percentage of their body weight supported by the harness. The body weight support was gradually decreased, and the training speed was increased over the period of 15 sessions. Two therapists provided manual assistance for the movements of the affected extremity and pelvis. The amount of assistance at each bout was reduced in a single session (Table 4.2).

All stroke survivors underwent gait analyses of the paretic leg during over-ground walking at their self-selected speed, as well as a clinical examination before training (baseline) and immediately after training (post-training). Each clinical evaluation session included lower-extremity Fugl-Meyer Assessment (FMA), Functional gait assessment (FGA), Six-Minute Walk Test (6MWT), and Timed Up and Go test (TUG).

Table 4.2 Training Protocol for Each 5-minute Bout During 15 Sessions of BWSTT.

	Bout 1	Bout 2	Bout 3	Bout 4	Bout 5	Bout 6	Bout 7	Bout 8
Day 1	40% PS	40% PS	40% PS	40% PS	40% PS	40% PS	40% PS	40% PS
Day 2	40% PS	40% PS	40% PS	40% PS	40% PS	40% PS	30% PS	30% PS
Day 3	40% PS + 0.1	40% PS + 0.1	40% PS + 0.1	40% PS + 0.1	30% PS + 0.1	30% PS + 0.1	30% PS + 0.1	30% PS + 0.1
Day 4	30% PS + 0.1	30% PS + 0.1	30% PS + 0.1	30% PS + 0.1	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2
Day 5	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	20% PS + 0.2	20% PS + 0.2
Day 6	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	30% PS + 0.2	20% PS + 0.2	20% PS + 0.2	20% PS + 0.2	20% PS + 0.2
Day 7	20% PS + 0.2	20% PS + 0.2	20% PS + 0.2	20% PS + 0.2	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3
Day 8	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	10% PS + 0.3	10% PS + 0.3
Day 9	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	20% PS + 0.3	10% PS + 0.3	10% PS + 0.3	10% PS + 0.3	10% PS + 0.3
Day 10	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4
Day 11	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	0% PS + 0.4	0% PS + 0.4
Day 12	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	10% PS + 0.4	0% PS + 0.4	0% PS + 0.4	0% PS + 0.4	0% PS + 0.4
Day 13	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5
Day 14	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.5	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6
Day 15	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6	0% PS + 0.6

4.3.4 Data Analysis

To understand the effects of gait training on footpath control we used the uncontrolled manifold (UCM) analysis. As discussed in the previous chapter the UCM approach allows us to understand how the CNS uses the variability of joint motions or muscles' activation across cycles to stabilize a task variable [47]. In the current study we sought to understand the relationship between groups of co-activated muscles called muscle modes and the footpath stability across gait cycles. To determine the contribution of muscle modes in footpath stabilization, three steps were taken.

Step 1: Non-negative matrix factorization

To compute the muscle modes we used non-negative matrix factorization (NNMF). The normalized linear envelope was used for computation of muscle modes using the NNMF [43]. EMG data from all the gait cycles was concatenated together to compute muscle modes across time. NNMF factors the concatenated original EMG data (V) into two matrices. The matrix W corresponds to the mode structure, and specifies the relative contribution of each muscle to a muscle mode and the matrix H is the activation timing of each muscle mode across a gait cycle. The number of adequate modes required for reconstructing the concatenated original EMG after data reduction was based on variability accounted for (VAF). VAF was computed as the sum of squared errors divided by the sum of squared original data as shown in equation (1).

$$VAF = \frac{1-\left(V-(W\times H)\right)^2}{V^2} \qquad (1)$$

The analysis starts with the assumption that only one mode is sufficient to reconstruct the EMG data. The number of modes was increased until a VAF > 90% was achieved for each of the ten muscles [17].

Step 2: Linear Regression

To determine how changes in the modes (ΔH) are related to the changes in the footpath (ΔFoot) during swing phase, regression analysis was used. The regression equation for the changes in the vertical position of foot during swing phase related to changes in the muscle modes was given as equation (2):

$$\Delta Foot_z = C_{1z}\Delta H_1 + C_{2z}\Delta H_2 + C_{3z}\Delta H_3 + C_{4z}\Delta H_4 \qquad (2)$$

The equation for the AP position of foot was given as equation (3):

$$\Delta Foot_{AP} = C_{1AP}\Delta H_1 + C_{2AP}\Delta H_2 + C_{3AP}\Delta H_3 + C_{4AP}\Delta H_4 \qquad (3)$$

Here $C_{1,}$ $C_{2,}$ $C_{3,}$ and C_4 are the regression coefficients in case of four modes. The coefficients were computed at each sample across multiple time-normalized gait cycles used to compute the Jacobian (J) = [$C_{1,}$ $C_{2,}$ $C_{3,}$ C_4].

Step 3: Uncontrolled Manifold Analysis

The Jacobian matrix was used for further analysis to compute how much of the muscle mode variance leads to variability of the footpath (V_{ORT}) or reflects flexible combinations of the muscle modes that produced a consistent footpath (V_{UCM}) using the UCM approach [47]. We computed the null space of the Jacobian (ε), which represents changes in the modes across gait cycles that lead to a consistent footpath. This null space is defined as the UCM subspace. The DOF for the UCM subspace is n-d where n is the number of modes. The foot path accounts for two DOF (d) for the vertical and AP positions. The mean-free mode data ($\Delta H_{mean\ free}$) was projected into the UCM subspace (equation 4):

$$UCM = \sum_{i=1}^{n-d} \left(\varepsilon \times \Delta H_{mean\ free}\right) \qquad (4)$$

and orthogonal subspace (equation 5):

$$ORT = \left(\Delta H_{mean\ free} - \varepsilon^T \times UCM\right) \qquad (5)$$

The variance in the UCM subspace (V_{UCM}) was computed per DOF at each data point averaged across all gait cycles (N) (equation 6):

$$V_{UCM} = \frac{1}{N}\frac{1}{n-d}\sum_{i=1}^{N}\left(UCM^2\right) \qquad (6)$$

Variance in the subspace orthogonal to the UCM space, or V_{ORT}, was computed at each data point per DOF of the orthogonal space (d) (equation 7):

$$V_{ORT} = \frac{1}{N}\frac{1}{d}\sum_{i=1}^{N}(ORT^2) \quad (7)$$

The relative difference (ΔV) between the two variance components is computed (equation 8).

$$\Delta V = \frac{V_{UCM} - V_{ORT}}{V_{UCM} + V_{ORT}} \quad (8)$$

ΔV with a value close to positive one suggests greater ability of an individual to stabilize the footpath. For statistical purposes, the average of variance components and relative variance difference is taken across the swing phase for each subject.

4.3.5 Statistical Analysis

Due to the small sample size, we used the non-parametric Wilcoxon signed rank test to test for within group differences in the gait parameters, clinical outcome measures, mode structure, mode timing, and relative variance difference between the evaluation sessions (i.e., baseline and post-training). The between group differences were tested using the Mann Whitney U test. Pearson's correlation was performed to compare the differences in the mode structure and timing between stroke survivors and matched controls at baseline and post-training. Mode quality is defined by the correlation coefficient with value of 1.0 as the perfect match between the stroke survivor and the matched control. The significance level for all statistical analysis was set at $p<0.05$. All statistics were performed in SPSS version 21 (IBM Co., Somers, NY).

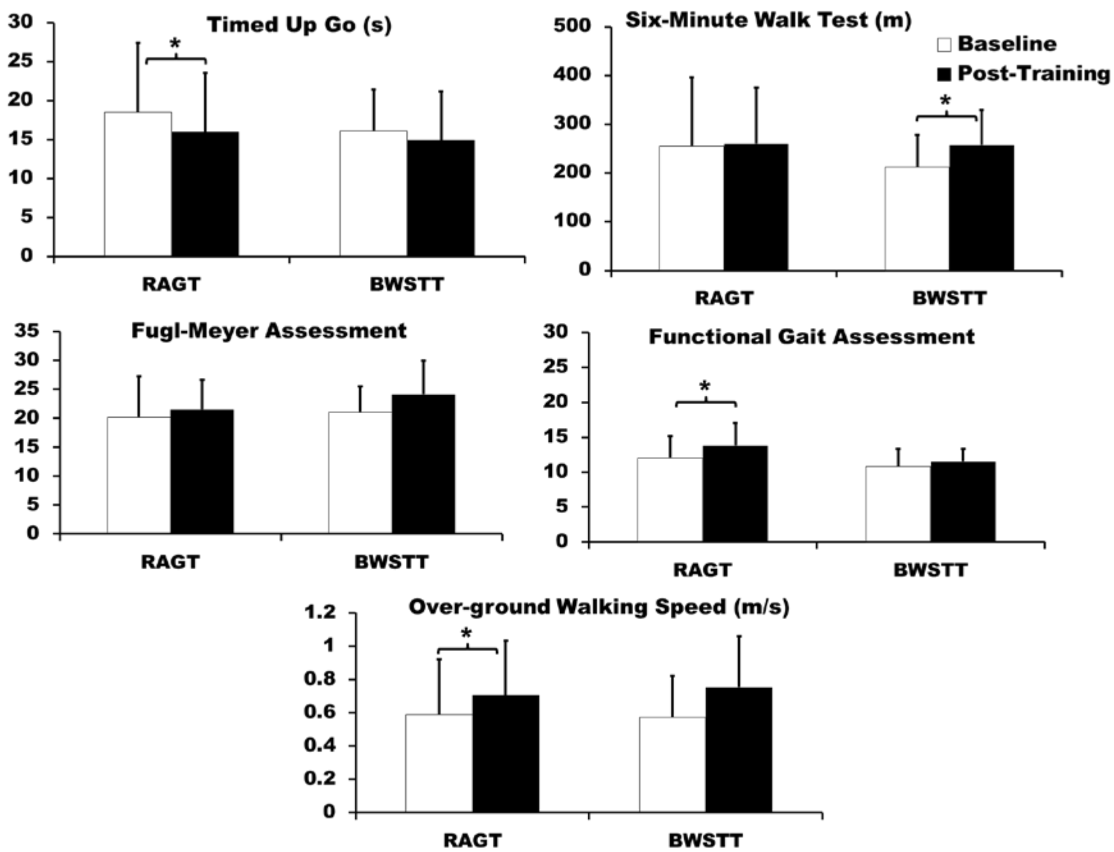

Figure 4.1 Clinical measures averaged across subjects for RAGT (right) and BWSTT (left) groups, at baseline and after training (post-training). Error bars represent the standard deviation across subjects. * $p<0.05$.

4.4 Results

4.4.1 Clinical and Kinematic Measures

Stroke survivors in the RAGT group exhibited significant changes following training in their self-selected over-ground walking speed ($p=0.02$; baseline=0.58±0.3 m/s; post-training=0.70±0.3 m/s), TUG ($p=0.02$; baseline=18.52±8.8 s; post-training=15.99±7.5 s), and FGA ($p=0.02$; baseline=12±3.1; post-training=13.83±3.1) (Figure. 4.1). However, no significant changes were seen in FMA ($p=0.34$;

baseline=20.16±7.1; post-training=21.50±5.1), and 6MWT (p=0.60; baseline=255.02±141.3 m; post-training=259.58±116.2 m). Peak knee flexion angles changed significantly following RAGT (p=0.02; baseline=43.87±18.7; post-training=48.12±17.4), but no significant changes were observed in the peak hip flexion angles (p=0.17; baseline=13.90±8.6; post-training=16.84±5.3) or peak ankle dorsiflexion (p=0.75; baseline=2.85±6.4; post-training=3.16±5.1) during swing phase (Figure. 4.2).

Individuals receiving BWSTT demonstrated improvements in 6MWT (p=0.04; baseline=211.73±66.1 m; post-training=257.85±71.6 m). However, no changes were seen in over-ground walking speed (p=0.07; baseline=0.57±0.2 m/s; post-training=0.75±0.3 m/s), TUG (p=0.46; baseline=16.12±5.3 s; post-training=14.95±6.2 s), FGA (p=0.46; baseline=10.83±2.4; post-training=11.50±1.8), and FMA (p=0.05; baseline=21±4.5; post-training=24.16±5.7) (Figure. 4.1). Furthermore, no significant changes were seen in the peak knee flexion angles (p=0.34; baseline=34.59±14.2; post-training=38.09±14.3), peak hip flexion angles (p=0.91; baseline=19.88±9.8; post-training=19.69±12.0), and peak ankle dorsiflexion (p=0.91; baseline=5.93±6.3; post-training=6.35±7.4) during swing phase (Figure. 4.2). There were no significant differences between the groups at baseline and following training.

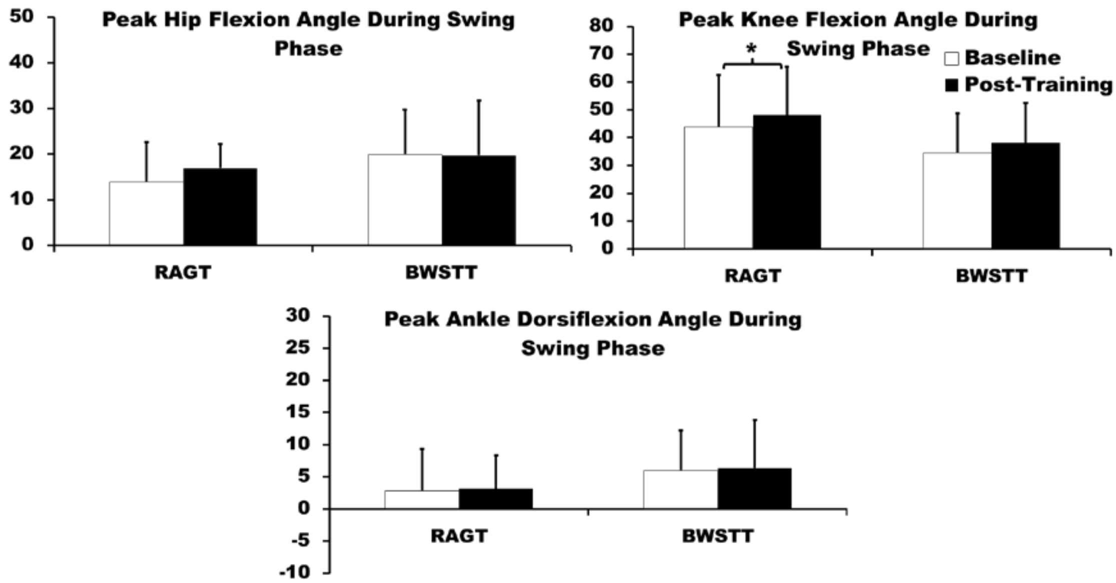

Figure 4.2 Peak hip and knee flexion angles and peak ankle dorsiflexion angle (°) during the swing phase of gait cycle averaged across subjects for the paretic leg for RAGT (right) and BWSTT (left) groups, at baseline and after training (post-training). Error bars represent the standard deviation across subjects. * p<0.05.

4.4.2 Muscle Modes and Relative Variance Difference

All healthy individuals needed four modes to explain 90% or more variance accounted for (VAF) for each of the ten muscles. Five out of six stroke subjects in each group demonstrated four modes while one subject in each group had three modes. Individuals following RAGT demonstrated improvements in the structure of one of the four modes (p=0.04; baseline=0.69±0.1; post-training=0.74±0.1). This mode primarily consisted of activity of tibialis anterior and rectus femorus muscles. However, no changes were seen in the activation timing of any mode following RAGT. Furthermore, stroke survivors did not demonstrate any changes in mode structure or mode activation timing following BWSTT. Relative variance difference (ΔV) improved significantly (p=0.04; baseline=0.31±0.1; post-training=0.45±0.1) following BWSTT, but no changes were seen in the ΔV after RAGT (p=0.34; baseline=0.46±0.3; post-training=0.47±0.2). In addition, no significant differences between the groups at baseline and following training were observed (Figure. 4.3).

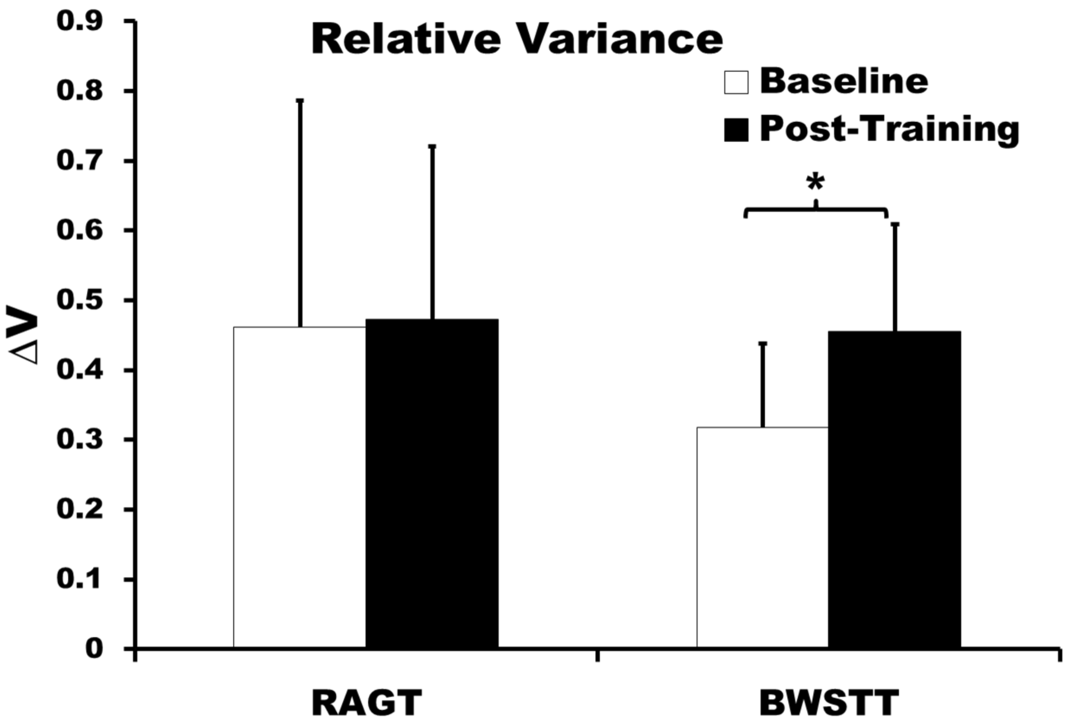

Figure 4.3 Relative variance (ΔV) during swing phase averaged across subjects for the paretic leg for RAGT (right) and BWSTT (left) groups, at baseline and after training (post-training). Error bars represent the standard deviation across subjects. * p<0.05.

4.5 Discussion

There were no significant changes in clinical or kinematic measures between the two groups following gait training. Nonetheless, individuals in both groups demonstrated within group improvements in some of the clinical and kinematic measures. Stroke survivors receiving RAGT with an assist-as-needed paradigm improved their mode structure to some extent, but did not show significant improvements in their ability to stabilize the footpath during the swing phase of walking. However, improvements in the footpath stabilization following BWSTT were significantly different following training.

Previous studies demonstrated that BWSTT and conventional gait training result in better improvements of functional walking ability post-stroke compared to the RAGT with continuous assistance [32, 124]. In the current study we compared the effects of BWSTT with RAGT using a performance based assist-as-needed paradigm which has not been done previously. In the current experiment stroke survivors receiving BWSTT did not demonstrated improvements in any clinical measures other than 6MWT after training. However, S7 demonstrated large improvements in the 6MWT compared to the other individuals following BWSTT. Therefore, it is possible that this particular subject may have skewed the data towards significant improvements. These results do not agree with previous studies, where improvements have been shown in self-selected walking speed, FMA, and 6MWT post-stroke following BWSTT [20, 32]. However, subjects' baseline walking speed and endurance in the current study was higher than the subjects in previous studies. In the current experiment, individuals receiving RAGT demonstrated improvements in their self-selected walking speed, TUG scores, and FGA scores following training. However, no significant changes were seen in 6MWT and FMA scores after training. The assist-as-needed training paradigm requires more physical effort than the continuous assistance [42], but there is still some possibility of subjects relying on the assistance provided by the assist-as-needed paradigm [146]. Therefore, a more challenging training paradigm may be needed for improvements in the endurance and sensory motor impairment following RAGT. There were no significant differences between groups following training. Furthermore, the subjects in both groups were less impaired compared to the subjects in a previous study demonstrating significant improvements following BWSTT and RAGT [20]. Therefore, future studies with a larger sample size and stroke survivors with diverse levels of motor impairments are needed to understand the differences between the two training paradigms post-stroke.

Results from previous studies are primarily based on the clinical measures for gait [32, 147]. In the current study we have compared the effects of BWSTT with an assist-as-needed gait training paradigm on over-ground walking pattern in addition to the clinical measures. This provides us with additional information regarding over-ground transfer of the effects of gait training on walking pattern of stroke survivors. None of the kinematic measures improved following BWSTT, but stroke survivors showed improvements in their peak knee flexion angles during the swing phase following RAGT. Individuals have a reduced peak knee flexion during the swing phase post-stroke which may be associated with increased energetic cost resulting from compensatory strategies used by stroke survivors [11]. Therefore, an increase in the peak knee flexion angle during swing following RAGT may help stroke survivors walk in a pattern that is closer to normal and more efficient. Previous studies have demonstrated an increase in the peak knee flexion during the swing phase in treadmill walking following an assist-as-needed robotic-gait training [31] as well as FES of platarflexors and dorsiflexors [148]. Therefore, it is difficult to determine whether the therapeutic effects shown in the current study were a result of a single component of the RAGT paradigm or a combined effect of all the components. Further investigation is needed to determine whether the improvements in peak knee flexion during swing following RAGT were due to the effects of the compliant force field, or FES, or both.

The relative variance difference (ΔV) defined as the ratio of the difference between the two variance components (V_{UCM} and V_{ORT}) and their sum, increased significantly following BWSTT. These results agree with the previous literature based on healthy individuals suggesting that practice can lead to an increase in ΔV [88, 149]. However, no changes were seen in the ΔV following RAGT. Subjects receiving RAGT had a higher ΔV at baseline (0.46±0.3) compared to the subjects in the BWSTT group (0.31±0.1) that increased to (0.45±0.1) following training. Therefore, subjects in the group receiving RAGT may have shown a ceiling effect for improvements in the footpath stabilization. In addition, S4 demonstrated a decrease in ΔV (baseline: 0.91; Post-training: 0.45) following RAGT training. The large amount of decrease in ΔV for S4 may have led to the skewing of the averages in the RAGT group. However, the decreased ΔV post-training is closer to normal (0.50±0.1). Therefore, the decrease in the ΔV for S4 following RAGT may be considered as a positive effect of training. The muscle mode structure changed towards healthy controls for the mode representing the contribution from tibialis anterior and rectus femorus muscles following RAGT, but no changes in the mode timing or number of modes were observed. In addition, no changes in the mode structure or timing were seen for any of the modes following BWSTT. A recent study has shown an increase in the number of muscle modes following BWSTT [89]. However, subjects received training for 36 sessions in the aforementioned study compared to 15 sessions in the current study. Furthermore, in the current study most of the subjects had four modes which is similar to the number of modes in healthy individuals. Therefore, more impaired stroke survivors receiving a greater number of training sessions may demonstrate improvements in the number of muscle modes following gait training.

4.6 Conclusion

The results from this study suggest that RAGT using an assist-as-needed paradigm may improve the clinical and kinematic measures of gait post-stroke to some extent. Though there were no significant differences between the two groups, RAGT is less labor intensive for physical therapists in comparison to BWSTT. Therefore, this performance based RAGT may be used as an alternative rehabilitation strategy to improve functional walking ability and gait pattern post-stroke. Furthermore, improvements were seen in the ability to stabilize the footpath during swing phase in stroke survivors following BWSTT. However, subjects in the RAGT group had a more stable footpath at baseline in comparison to BWSTT group. Future studies are needed to identify the effects of RAGT on stroke survivors with more impaired coordination in comparison to healthy individuals.

Chapter 5

CONCLUSION

The overall goals of this dissertation were to understand the footpath control in stroke survivors and non-neurologically impaired individuals, and to compare the effects of robot-aided gait training with body weight supported treadmill training on coordination of footpath and walking ability post-stroke. The results from this dissertation suggested that the footpath is an important task variable during swing phase of walking in healthy individuals as well as stroke survivors. In addition, stroke survivors benefit from robot-aided gait training (RAGT) and body weight supported treadmill training (BWSTT) evidenced by improvements in some of their clinical and kinematic measures following either of the training methods. However, only the subjects receiving BWSTT demonstrated improvements in the footpath coordination following training. Furthermore, we did not see any significant differences in improvements between the two groups following training.

5.1 Major Findings

5.1.1 Footpath Stabilization During Swing Phase of Walking

The uncontrolled manifold (UCM) analysis was used to understand the relationship between muscle mode variance and the variance of footpath across gait cycles. A previous study has looked at the stabilization of the medio-lateral foot position during walking using the UCM approach [1]. However, in the current study we are trying to understand the stabilization of foot in the vertical and antero-posterior position during the swing phase of walking which is critical in minimizing falls. The results of Aim 1 were consistent with our hypothesis showing that the V_{UCM} or the variability of the muscle modes leading to a consistent footpath was significantly larger than V_{ORT} or the muscle mode variability resulting in an inconsistent footpath across cycles in non-neurologically impaired individuals during the swing phase of walking. This suggests that footpath is an important task variable and healthy individuals stabilize their foot position during swing phase of walking.

Individuals following stroke often have impaired joint and muscle coordination. Previous studies have shown that this impaired coordination can affect the ability to stabilize an important task variable following a neurological injury [2, 3]. In the current experiment we tried to understand whether the stroke survivors were able to stabilize their footpath, and if their ability to stabilize footpath determined by relative variance difference was different from their age and gender matched control subjects. The results suggested that individuals retain the ability to stabilize the footpath following stroke. However, relative variance difference was not significantly different between non-neurologically impaired individuals and stroke survivors. Furthermore, the stroke population had greater total variance in comparison to their age and gender matched healthy controls. Therefore, impaired coordination and increased variance following stroke may not affect the ability of the stroke survivors to maintain a stable footpath during the swing phase of walking.

5.1.2 Effects of Robot-aided Gait Training Using an "Assist-as-needed" Paradigm on Stroke Survivors' Over-ground Walking Performance

RAGT with a novel assist-as-needed paradigm along with FES and a visual feedback of stroke subjects' instantaneous ankle path and a normal ankle path was used in the current experiment to rehabilitate the gait pattern post-stroke. This novel paradigm may encourage subjects' active participation and increases their physical effort as opposed to the previously used robotic training with continuous assistance. In the current study we tried to investigate the effects of this novel assist-as-needed gait training paradigm on the over-ground walking pattern post-stroke. The results of this study partially supported the hypothesis demonstrating that some of the clinical and kinematic measures were improved following training. These results agreed with previous pilot studies that demonstrated similar trends of improvements in the clinical measures [4, 5]. Furthermore, some of these improvements were retained 6 months following training. Therefore, based on the results in the current study, RAGT with a novel assist-as-needed paradigm may be considered as a potential method of gait rehabilitation post-stroke for improvements in over-ground walking pattern.

5.1.3 Robot-aided Gait Training vs Body Weight Supported Treadmill Training

This study compared the effects of the RAGT using an assist-as-needed paradigm with BWSTT. BWSTT is often used for gait training at an early stage post-stroke in clinical settings. Previously studies have been performed to compare the effects of BWSTT with robot-aided training using continuous assistance. These studies have suggested that robot-aided gait training has similar or poor effects in comparison to BWSTT [6, 7]. However, subjects tend to reduce their physical effort during continuous assistance. Therefore, an assist-as-needed training paradigm that encourages subject participation may have better effects on the improvements in gait patterns post-stroke. To our knowledge no previous study has compared the effects of BWSTT with RAGT using an assist-as-needed paradigm. In the current study we investigated the effects of RAGT in comparison to BWSTT on functional walking ability and the ability to stabilize footpath post-stroke.

The results from the current study suggested that subjects demonstrated improvements in their self-selected walking speed and walking balance following RAGT. Therefore, RAGT based on the ankle malleolus path may help in changing the gait pattern post-stroke. Furthermore, subjects demonstrated an increase in the peak knee flexion angle during swing which may result in a walking pattern closer to normal [8]. An increase in the peak knee flexion angle may also have led to increased foot clearance. In addition, subjects receiving BWSTT showed improvements in their walking endurance. However, no significant differences were observed between the two groups. Therefore, RAGT may improve the functional walking ability of individuals following stroke, and though these changes were not significantly different from the changes following BWSTT, RAGT may still be used as an alternate method for intensive gait rehabilitation as it is less laborious for the physical therapists compared to BWSTT.

Subjects receiving BWSTT improved their ability to stabilize the footpath during the swing phase of walking. No significant changes were seen in the footpath stability following RAGT. However, subjects receiving RAGT had a higher relative variance difference at baseline which was closer to healthy individuals compared to the subjects receiving BWSTT. This suggests that subjects in the RAGT group were better able to stabilize their footpath before training. Based on these results we can conclude that gait rehabilitation may improve the footpath stability during walking post-stroke in individuals with poor footpath coordination. However, due to the small sample size and less impaired stroke survivors in the current study it is hard to determine whether one training paradigm may be more or equally effective than the other in improving their ability to stabilize footpath.

5.2 Future Work

5.2.1 Footpath Stabilization During Swing Phase of Walking

In the current study we demonstrated that the healthy individuals and stroke survivors were able to stabilize their foot in the vertical and antero-posterior position during the swing phase of walking. We have included the muscles of the swing limb in the current analysis. However, it is possible that the muscles of the stance limb may also influence the foot position. Therefore, future studies may be needed to understand the relationship between the variability in muscle modes of both limbs on the footpath stabilization of the swing limb in healthy and neurologically injured individuals. Furthermore, future work is needed to identify the relation between impairment levels and the ability to stabilize the footpath post-stroke which may help us in identifying fallers in the stroke population.

5.2.2 Effects of Robot-aided Gait Training Using an “Assist-as-needed” Paradigm on Stroke Survivors' Over-ground Walking Performance

In the current study we investigated the effects of RAGT with a compliant force field and visual feedback of the ankle malleolus and functional electrical stimulation of plantarflexors and dorsiflexors. The improvements can be considered as the combined effect of all three components. Therefore, future studies are needed to determine whether one component of the training paradigm may be more effective than the others. Furthermore, we have only nine subjects in this study, so future studies with a larger sample size are needed to understand the effects of RAGT with the assist-as-needed paradigm in the stroke population.

5.2.3 Robot-aided Gait Training vs Body Weight Supported Treadmill Training

This pilot study compared the effects of the performance based RAGT using a compliant force-field with BWSTT. Both groups demonstrated improvements in some measures following training. However, stroke survivors in both groups had a lower impairment level in comparison to previous literature [6]. Therefore, future studies including subjects with a wider range of impairment levels will help us understand the effect of RAGT in comparison to BWSTT in stroke survivors. Additionally, comparisons of the novel RAGT paradigm used in the current study with conventional physical therapy treatment or the prototype RAGT with continuous assistance may provide further information regarding its effectiveness compared to the traditionally used treatment paradigms.

This dissertation work was the first attempt to understand the role of muscle modes in stabilizing the vertical and antero-posterior foot position using the UCM approach. Furthermore, we also compared the effects of BWSTT with a performance based RAGT on over-ground walking pattern and footpath stabilization which had not been investigated previously. Though results from this work are based on a small sample size, however it provides us with preliminary information based on which further research can be pursued to develop efficient gait rehabilitation strategies for individuals with neurological injuries.

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Appendix

IRB Approval Documents

INFORMED CONSENT FORM

STUDY TITLE: [159674] ROBOTIC EXOSKELETONS, FES, AND BIOMECHANICS: TREATING MOVEMENT DISORDERS

Principal Investigators: Jill Higginson, PhD

You are invited to participate in a research study to explore changes in walking patterns.

- Persons without neurological problems will be asked to participate in either one or three experimental sessions, depending on the study, at the University of Delaware.
- Stroke survivors will be asked to participate in as many as 33 visits to the University of Delaware for evaluation and training.

All sessions will take place at the Science, Technology and Applied Research building at the University of Delaware and will take approximately 2.5-3 hours. Participation in this study is voluntary. You may withdraw from this study at any time without any consequences. If you are a stroke survivor and have other conditions that may affect your ability to exercise or to learn, you should let us know. If you have severe respiratory problems such as chronic obstructive pulmonary disease (COPD), heart disease, a loss of sensation, uncontrolled blood pressure, a seizure disorder, severe arthritis, or other lower extremity orthopedic conditions that limit your activity level, you should not participate in this study.

CLINICAL EVALUATION: Stroke survivors will participate in two clinical evaluations, one before and one after training is completed. These evaluations will evaluate the following abilities:

1. Your ability to produce different leg movements while in different positions, and to perform basic functions such as rolling from lying to sitting, and walking.
2. Your balance while standing on either one or both legs and with both eyes open and closed.
3. Your balance while standing while you perform other actions such as reaching or stepping in different directions with your foot.
4. Your ability to walk while performing other activities such as looking around, stepping over objects, and changing speeds.
5. The resistance of your limbs when moved passively by the evaluator while you try to relax
6. Your ability to remember different number or word sequences and various historical events.

7. Your ability to tell the difference between objects of different shapes and orientations.
8. Your ability to perform common activities necessary for daily function, including bowel and bladder function, as assessed through a questionnaire.
9. Your ability to feel touch, pressure, where your joints are positioned and, how they are moved.

You will also be asked to provide signed permission to contact your physician for medical records related to your stroke, and other medical history that might adversely affect your ability to perform the required training. If you are a candidate to participate in the control group of persons without a stroke, you will be questioned about your current health status. Only if you report that you have another suspected or actual neurological problem, or a condition that has the potential to be associated with a neurological problem such as diabetes or chronic dizziness, will you also receive the clinical evaluations outlined for the stroke participants, as described above.

EXPERIMENTAL EVALUATION: Movement of your joints and your muscles' activity will be recorded while you walk either on a treadmill or during over ground assessments, as well as during strength tests that require you to push your foot against an immovable object. This requires that (1) markers be attached to your skin with sticky-backed Velcro and (2) muscle sensors be attached to your skin with double-sided, hypoallergenic tape. These evaluations will be performed before training begins, midway through the training, and following the completion of training. _________YES.

☐ ***Healthy Adult Adaptation Training (One experimental session)***: If you are one of the forty-eight (48) persons without a neurological problem who agree to participate in this arm of the study, investigating adaptation to walking with a different footpath, you will participate in one training session. During the session, you will wear an automated brace that is custom-fitted and attached to your leg. The motorized brace is designed to apply gentle forces that help direct your foot's movement toward a different footpath while you walk on the treadmill. Your typical footpath will be determined during walking while wearing the brace prior to training, but without it being activated. The experimenters then will prescribe a new footpath that is based on modifying your typical footpath. You will be asked to figure out and produce the modified footpath while walking on the treadmill. Your task will be to try to match the new footpath during training trials. The new, prescribed footpath may or may not be displayed on a video screen located in front of you. During training trials, a gentle force will be applied to your leg that either (1) tends to move you towards the new footpath if you deviate too far from that footpath or (2) tends to push your foot further away from the new footpath if you deviate from it. You will either be asked to try to stay within the newly prescribed footpath ***or to try to maintain your typical footpath despite the tendency of the brace to pull you towards the newly prescribed footpath***. You will also walk on the treadmill without any applied force during the experimental session.

In addition, your stepping will be assessed from recordings of markers placed on your shoe while walking over ground both before and after training on the treadmill. In all, testing and training will take about 2-hours.
____________YES.

☐ ***Long-term training:*** If you are one of thirty-six (36) stroke survivors who will receive long-term training, you may be asked to participate in an initial strength-training program that involves three training sessions per week for 3 weeks. The sessions will include exercise and electrical stimulation of your leg muscles to help increase your muscle strength. The main training sessions, which will occur after strength training if you receive that, will consist of between 12 and 18 sessions of walking training. The 12-18 sessions of walking training will take place over a period of 6 weeks using one of the first three training protocols listed below. Your protocol will be selected through a process of random assignment. Each training session will at total of 2.5-3. However, the actual time you will spend doing walking training 40 minutes, performed in eight 5-minute periods.
____________YES.

<u>Training Protocols</u>: Only the protocol with the check-mark in the box applies to you.

1. ☐ Practice walking on a treadmill while your body weight is supported by a suspension system. The amount of body-weight support will be reduced as your walking improves. Therapists will assist your leg movement during some portions of the training to help give you the sense of the desired walking pattern.
____________YES.

2. ☐ Practice walking on a treadmill assisted by a passive leg brace that removes the influence of gravity from your leg, combined with electrical stimulation of your ankle muscles to aid their contraction, and visual feedback about your performance. The amount of gravity balancing of your leg will be gradually reduced over training as your walking improves. ___________YES.

3. ☐ Practice walking with the assistance of a motorized leg brace that can apply gentle forces to your leg to help you produce more normal joint and foot movements of your impaired leg combined with functional electrical stimulation of your ankle muscles to help them contract, and visual feedback about your performance. Gentle forces applied to your leg by the motors will help your foot move in a more normal pattern (displayed to you a video monitor) and provide a spring-like resistance to your foot if it moves too far away from the prescribed joint or foot paths. The amount of assistance will be reduced over training as your walking improves.
______YES.

4. ☐ For this pilot study, you will be one of **twelve** stroke survivors and twelve individuals without neurological impairment who will walk both over ground and on a treadmill so that we can evaluate the coordination of your joints and muscles in relation to how you control the path of your foot and/or body position during walking. Stroke survivors will walk on the treadmill both with and without a motorized brace applied to one your impaired leg. Most subjects without neurological impairment will walk on the treadmill without the brace attached, but some subjects may also be asked to walk with the brace. Your joints' motions will be recorded with a camera system by placing reflective markers on your skin. Your muscle activity will be measured by placing muscle activity sensors on your skin over muscles of interest.
______YES.

a. ☐ <u>Stroke Survivors</u>: If you are a stroke survivor, you will participate in five daily training sessions for either one week or three weeks, with each of three weeks separated by one week rest from training, where you practice walking with the assistance of a motorized leg brace that can apply gentle forces to your leg to help you produce more normal joint and foot movements with your impaired leg. Visual feedback also will be provided about your performance. For some stroke survivors, functional electrical stimulation may be applied to your ankle muscles to help with ankle control. During training trials, a gentle force will be applied to your leg that tends to either push your foot further away from or closer to the desired footpath when you deviate from it. As long as you stay within the designated footpath, a force will not be applied. Thus, you will be asked to try to stay within the newly prescribed footpath and avoid the force being applied to your leg. Each daily session will be composed of eight 5-minute bouts of walking, for a total of 40 minutes, with rest provided between training bouts. In addition, one baseline, mid-training (after three training bouts) and post-training bout of walking will be obtained without any forces applied to your leg to evaluate changes in your gait pattern. For those who are willing, we will have you return two weeks after this initial training for comparable sessions of training using the opposite force training protocol (i.e., assistance versus resistance). If you are unwilling to do this, you can still participate in the initial training protocol.

b. ☐ <u>Control Subjects:</u> If you are a subject without neurological impairments, you may be asked to come for either one or two experimental sessions. As noted in #4 above, you may be asked to walk with or without a motorized brace attached to your leg. However, if you are asked to walk with the brace, no forces will be applied to your leg and only the motions of your joints and your muscle activity will be recorded for comparison to the same data from the stroke survivors. Each session will involve approximately 20 minutes each of walking over ground and on the treadmill, with rest breaks as needed.
______YES.

☐ **ELECTRICAL STIMULATION:** If you are a participant recovering from a stroke and participating in training protocols 2 or 3, electrical current will be delivered to the muscles in front of and at the back of your leg as you walk. Initially, a low level electrical current will be delivered through the plates to ensure that you are comfortable with the sensation of the stimulation. You will feel a "prickly" sensation on your skin or feel as if your muscle is being squeezed, but you should not feel pain. You will be asked to walk while the computer applies the electric current to your muscles. The current will be adjusted depending on how well you can activate the muscle yourself. However, the stimulation should never be painful. ______ ______YES

<u>**RISKS AND BENEFITS**</u>**:** The risks associated with the motion analysis evaluations and measures of muscle activity include a possible mild skin reaction to the tape used to attach the markers and sensors to your skin and falling while performing the tasks. However, a trained researcher will monitor you at all times to prevent a fall.

It is possible that we will discover functional impairments during the evaluation that have not been previously identified or brought to your attention. Although this may be worrisome, such information may help you obtain treatment to correct or improve the impairments. The decision as to whether to share any such information with your physician or others will be up to you.

There is a risk of injury from walking with the motor-actuated brace attached to your leg. This risk is minimized in several ways. The motor controller of the device is designed to gently assist your leg's movement by applying only small forces. The motors are set to limit the amount of applied force to the minimum amount needed to assist the motion and if forces exceed these values, the motors are automatically shut off. In addition, physical stops on the brace prevent motion beyond your normal range of joint motion. Both you and the investigator will have a switch that can be pushed to immediately shut down the motors. Nonetheless, it will be important for you to inform the investigators immediately if you perceive uncomfortable forces being applied to your leg. If you experience any discomfort, the motors will be immediately stopped and appropriate adjustments made to reduce the forces. You may also experience general muscle soreness following the walking evaluations, particularly if you have not been exercising regularly.

Pressure from the links of the brace that assist your leg movement can occur due to faulty alignment, which may result in irritation and redness of the skin. The same is true of the harness support if you are participating in body-weight supported treadmill training. Aligning the brace or the support cuffs for each participant individually reduces these risks. *However, it is important that you inform the investigators if you are experiencing any unusual pressure from the brace or support cuffs while wearing them so that proper adjustments can be made.*

Some subjects report muscle soreness for about 2 days after electrical stimulation that is similar to the muscle soreness you might feel if you lift weights or exercise vigorously after a long lay-off. During some stimulation you may feel pain in your

thigh and/or calf muscles similar to what you may experience when bicycling hard up a long hill. The sensation of pain and fatigue will subside soon after the end of the stimulation. Although there is a possibility of injury such as muscle strain, muscle tear, injury of the kneecap or injury to other bones of the leg, this is highly unlikely. The potential for equipment malfunction is also present, which might result in burns to the skin. It is important that you inform us if you experience a sensation of burning or pain under the stimulation electrodes so that we can immediately stop the electrical stimulation.
The benefits from participating in this study if you are a stroke survivor include comprehensive evaluation sessions and intensive training designed to help improve your walking pattern. However, we cannot guarantee that your walking pattern will improve.

Your participation, whether as a patient or healthy adult, may provide valuable information that will help in the design and application of new technology although this may be of no direct benefit to you. This information may help us to improve the way we treat future stroke patients.

CONFIDENTIALITY
Personal information and the associated case number will be stored in a locked file cabinet in the laboratory. Data will be associated directly with the case number alone, not the personal information. Only the researchers will have access to this information. Your individual evaluation results will not be shared with anyone outside the laboratory except you. If you give us written permission, we will also share the results with your physician. Neither your name nor any identifying information will be used in any publication or presentation resulting from this study. The data collected about your walking performance during these studies will be saved on long-term storage media such as CDs or DVDs, without information that can directly identify you. The media will be stored in the investigator's laboratory at the Science, Technology and Applied Research campus. Following completion of this project (approximately five years), the data will be destroyed or stored in a secured file cabinet in the investigators' laboratory if the information is deemed to continue to be useful to explore future clinical questions.

PATIENT'S STATEMENT
I have read this consent form and have discussed the procedure described above with the investigator(s). I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any further questions that I might have will be answered verbally, or if I prefer, with a written statement.
If you are injured during research procedures, you will be offered first aid at no cost to you. If you need additional medical treatment, the cost of this treatment will be your responsibility or that of your third-party payer (for example, your health insurance).

By signing this document you are not waiving any rights that you may have if injury was the result of negligence of the University or its investigators.
I have been fully informed of the above-described procedure with its possible risks and benefits, and I hereby consent to the procedures. I have received a copy of this consent form.

____________________________ ________________
Subject's signature Date

____
Subject's Name (please print)

____________________________ ____________
Investigator's Signature Date

If you have any questions concerning your rights as a research participant, you may contact the University of Delaware Human Subjects Review Board (831-2137). Questions regarding the clinical evaluations or leg-brace portions of the study may be addressed to Dr. Higginson (302) 831-6622. Questions about the electrical stimulation may be addressed to Dr. Binder-Macleod (302) 831-8046.

*Personal Physician Information

____
Name

____
Street Address

____
City, State and zip code

____
Phone number

By signing below, I give the investigators permission to contact my physician to obtain pertinent medical records about me.

____________________________ ________________
Subject's signature Date

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	March 21, 2012
TO:	John Scholz, PhD, PT, MA, BS
FROM:	University of Delaware IRB
STUDY TITLE:	[159674-7] Robotic Exoskeletons, FES, and Biomechanics: Treating Movement Disorders (Previously "Evaluation and Training of Walking Ability Post-CVA", changed to match the title of the funded grant project)
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	March 21, 2012
EXPIRATION DATE:	April 15, 2013
REVIEW TYPE:	Full Committee Review

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Jody-Lynn Berg at (302) 831-1119 or jlberg@udel.edu. Please include your study title and reference number in all correspondence with this office.

UNIVERSITY OF DELAWARE

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	April 21, 2014
TO:	Jill Higginson, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[159674-14] Robotic Exoskeletons, FES, and Biomechanics: Treating Movement Disorders (Previously "Evaluation and Training of Walking Ability Post-CVA", changed to match the title of the funded grant project)
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	April 21, 2014
EXPIRATION DATE:	April 15, 2015
REVIEW TYPE:	Full Committee Review

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Maria Palazuelos at (302) 831-8619 or mariapj@udel.edu. Please include your study title and reference number in all correspondence with this office.