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An Analysis of Modular Patterns in Healthy and Post-stroke Hemiparetic Gait

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An Analysis of Modular Patterns in Healthy and Post-stroke Hemiparetic Gait

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Dedication

This dissertation is dedicated to my grandaunt Helen C. Devine who has inspired me.

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An Analysis of Modular Patterns in Healthy and Post-stroke Hemiparetic Gait

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Recent studies have suggested the biomechanical subtasks of walking can be produced using a reduced set of co-excited muscles or modules. Individuals post-stroke often exhibit poor inter-muscular coordination characterized by poor timing and merging of modules that are normally independent in healthy individuals. However, whether locomotor therapy can influence module quality (timing and composition) and whether these improvements lead to improved walking performance is unclear. Further, it is unknown whether the same modules that produce self-selected walking can also produce the execution of different mobility tasks.

In this study, experimental analyses were used to compare module quality pre- and post-therapy. In subjects with four modules pre- and post-therapy, locomotor training resulted in improved timing of the ankle plantarflexor module and a more extended paretic leg angle that allowed the subjects to walk faster with more symmetrical propulsion. In addition, subjects with three modules pre-therapy increased their number of modules and improved walking performance post-therapy. Thus, locomotor training was found to influence module composition and timing, which can lead to improvements in walking performance.

Experimental and simulation analyses were then used to characterize modular organization in specific mobility tasks (walking at self-selected speed with maximum cadence, maximum step length, and maximum step height). We found that the same underlying modules (number and composition) in each subject that contribute to steady-state walking also contribute to the different mobility tasks. In healthy subjects, module timing, but not composition, changed when the task demands were altered. This adaptability in module timing, in addition to the ability to adapt to the changing task demands, was limited in the post-stroke subjects. The primary difference in the execution of the walking biomechanical subtasks occurred in the control of the leg during pre-swing and swing. To increase cadence, the ankle plantarflexors and dorsiflexors contributed more power to the ipsilateral leg in pre-swing and swing, respectively. To increase step height, the hamstrings provided energy to the ipsilateral leg that accelerated the leg into swing in pre-swing and swing. These results provide a first step towards linking impaired module patterns to mobility task performance in persons post-stroke.

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Chapter 1: Introduction

BACKGROUND

Stroke is the leading cause of long-term disability in the United States (Roger et al. 2012), with hemiparesis persisting in 50 percent of survivors six months post-stroke (Kelly-Hayes et al. 2003). Post-stroke hemiparetic gait is frequently characterized by diminished speed, increased duration of stance on the non-paretic limb, increased duration of double support and asymmetric joint kinematics and kinetics between the paretic and non-paretic legs (Higginson et al. 2006; Richards 1996). Because improved walking ability is a priority in post-stroke rehabilitation (Dobkin 2005), assessments are needed to evaluate walking performance throughout the rehabilitation process. Previous assessments have compared self-selected walking speed (Bowden et al. 2008), propulsive and braking impulses (Bowden et al. 2006), paretic leg propulsion (Bowden et al. 2006), step length asymmetry (Allen et al. 2011; Balasubramanian et al. 2007; Hsu et al. 2003) and pre-swing leg angle (Peterson et al. 2010). However, these measures alone do not fully reveal how neuromuscular control improves a patient's walking performance, therefore alternative assessments are needed.

Since gait impairments are the result of deficient neuromuscular control, studies have recently focused on quantifying the neuromuscular control deficits exhibited by individuals post-stroke to gain insight into walking performance. Groups of co-excited muscles are often referred to in the literature as muscle modules or synergies. These modules are groups of muscles that are co-excited to perform a given task (Lacquaniti et al. 2013; Ting et al. 2007). Studies have investigated modules during movement in frogs (e.g., d'Avella et al. 2005; d'Avella et al. 2003; Hart et al. 2004; Kargo et al. 2008; Kargo

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Studies have also shown that a few sets of distinct muscle groups are sufficient to produce highly complex movements in humans, such as walking (Cappellini et al. 2006; Clark et al. 2010; Ivanenko et al. 2004; Neptune et al. 2009), running (Cappellini et al. 2006), walking with induced slipping (Oliveira et al. 2012), and running with cutting maneuvers (Oliveira et al. 2013), as well as, reaching (Cheung et al. 2009; Muceli et al. 2010), cycling (Hug et al. 2010; Raasch et al. 1997), and balance (Ting et al. 2007; Torres-Oviedo et al. 2006; Torres-Oviedo et al. 2007, 2010). In each of these activities, modules have been related to the generation of particular movements and are consistent across multiple tasks (Cappellini et al. 2006; Ivanenko et al. 2005; Oliveira et al. 2013). In addition, primitive stepping in newborn human babies can be represented by modules that are retained and modified towards those found in adults during the early years of development (Dominici et al. 2011), thus suggesting that modules are both innate and adaptive.

However, the existence and function of muscle modules has been disputed in the literature (Tresch et al. 2009). We and others interpret muscle modules as centrally coded, learned patterns of multi-muscle co-excitation that are efficient neural solutions to complex biomechanical demands and generate specific biomechanical functions (Clark et

al. 2010; Ting et al. 2005). However, this interpretation is not universal. Some believe that modules may develop due to optimal control (de Rugy et al. 2013) or emerge as the result of biomechanical constraints (Kutch et al. 2012). Recent studies have provided evidence against the existence of muscle modules in finger control (Kutch et al. 2008; Valero-Cuevas et al. 2009). Yet, the lack of modules found in the finger does not definitively prove that modules do not exist in all limbs or for all mobility tasks. For example, modules have still been used to explain movements of the arm (Krishnamoorthy et al. 2007) and hand (Ajiboye et al. 2009; Gentner et al. 2006). Therefore it is possible that non-specialized and repetitive movements, such as walking, may indeed be governed by modules.

Studies have shown that in animals, modules are encoded at the spinal level (Hart et al. 2010; Kargo et al. 2008; McCrea et al. 2008; Tresch et al. 2002). However, recent studies in humans showing impairment to independent activation of modules and diminished module quality following a stroke (Cheung et al. 2009; Cheung et al. 2012; Clark et al. 2010) suggest that supraspinal pathways may also contribute to module organization and control. Indeed, although central pattern generators do control gait at a spinal level, supraspinal control is needed for adapting locomotion, initiating stepping and stopping (Holtzer et al. 2014; Jahn et al. 2004; Yogev-Seligmann et al. 2008). Supraspinal regions primarily involved in locomotion include the motor cortex and the corticospinal pathway. However, the brain stem, cerebellum, hippocampus, and basal ganglia also play a significant role in human locomotion (Jahn et al. 2008; Jahn et al. 2004; Jahn et al. 2009). Each of these supraspinal regions likely has a role in the control and organization of muscle module patterns that are encoded within the spine. Thus, supraspinal controls are able to modify the recruitment of modules, which are the basic building blocks of motion, to vary activity in a task-specific manner. Indeed, stimulation

of different cortical sites has been able to produce low-dimensional hand movements (Gentner et al. 2006). Therefore, lesions to any supraspinal regions of the brain may result in poor organization and control of modules that can lead to the merging of normally independent modules and poor walking performance.

In healthy adults, experimental analyses of modular organization have shown that well-coordinated walking can be produced by exciting four co-excitation modules: Module 1 (hip and knee extensors) in early stance, Module 2 (ankle plantarflexors) in late stance, Module 3 (tibialis anterior and rectus femoris) during the stance to swing transition, and Module 4 (hamstrings) in the swing to stance transition. Essential biomechanical subtasks of steady state walking (e.g., body support, forward propulsion, leg swing and mediolateral balance control) have been shown to be produced by specific modules (Allen et al. 2012; Neptune et al. 2009). However, compared to healthy subjects, post-stroke hemiparetic subjects display poor inter-muscular coordination characterized by dissimilarity in module composition and timing from those of healthy subjects and often have a reduced set of modules (Clark et al. 2010). Post-stroke subjects tend to fall into one of three sub-categories (low, moderate and high complexity) based on their number of independent modules (Clark et al. 2010). Given that modules control the biomechanical subtasks of movement, a reduced set of modules suggests the biomechanical subtasks of walking may be interfering with one another. Greater interference between subtasks leads to poorer walking performance while less interference leads to better walking performance (Allen et al. 2013; Clark et al. 2010). A higher number of independent modules post-stroke has been associated with improved performance in various clinical and biomechanical assessments of walking, including increased walking speed, improved ability to change walking speed (increase from self-selected to fast walking speed), improved Dynamic Gait Index, and improved step length

and propulsion symmetry (Bowden et al. 2010; Clark et al. 2010). Even in those individuals who have four modules post-stroke, the modules differ in composition (i.e., the relative weighting of each muscle in each module) and timing (i.e., the activation of those modules over the gait cycle) from those of healthy individuals, which likely adversely affects their walking ability. Although it has been shown that the number of independent modules is important, it is also necessary to ensure that the quality of the modules is appropriate with regard to timing and composition. Indeed, individuals post-stroke who have an appropriate number of modules often exhibit walking deficits relative to healthy individuals (Clark et al. 2010). Therefore, improvement of the composition and timing of their modular organization such that it better matches the organization of healthy subjects could significantly improve locomotor performance.

STUDY GOALS

Whether locomotor therapy can improve module composition and timing and if these improvements lead to better walking performance is unclear (e.g., Den Otter et al. 2006). Therefore, the goal of the study in Chapter 2 was to examine the influence of a locomotor rehabilitation therapy on module composition and timing and walking performance in post-stroke hemiparetic subjects. Specifically, this study assessed whether those subjects with four modules pre-therapy improved their post-therapy module composition and timing and walking performance. In addition, module composition and timing post-therapy were compared in all subjects with four modules post-therapy, grouped by pre-therapy number of independent modules, to determine whether the number of modules an individual had pre-therapy influenced their post-therapy modular organization and biomechanical measures of gait performance. Specific measures of gait performance included self-selected walking speed, paretic step length asymmetry, paretic

pre-swing leg angle, and propulsion asymmetry. It was expected that subjects with improved module composition and timing would have improved walking performance as defined by increased walking speed, and a decrease in asymmetries between the paretic and non-paretic legs. Additionally, it was expected that subjects with fewer modules pre-therapy would have poorer module composition and timing and gait performance post-therapy than those who had a greater number of modules pre-therapy.

In addition to steady state walking, daily lower limb mobility is comprised of many diverse motor tasks such as accelerating, stopping, turning and avoiding obstacles. Studies investigating healthy individuals executing tasks, such as kicking a ball while walking (Ivanenko et al. 2005), running (Cappellini et al. 2006), walking with induced slipping (Oliveira et al. 2012), and running with cutting maneuvers (Oliveira et al. 2013), have identified module patterns similar to those during normal walking. Some of these studies have also revealed adaptability in module timing (Cappellini et al. 2006; Oliveira et al. 2013) or changes in the number of modules (Ivanenko et al. 2005) in response to changing task demands. A recent study hypothesized that the central nervous system adapts the existing spinally encoded module structure to task demands rather than introducing new modules (Oliveira et al. 2012). Because each module contributes to specific biomechanical functions in healthy walking (Allen et al. 2012; Neptune et al. 2009), it is expected that mobility tasks that require specific changes in biomechanical function will affect corresponding module patterns and timings. Thus, a lack of independent modules or a lack of ability to change the timing of a specific independent module, commonly seen in subjects post-stroke, could affect a subject's ability to execute a specific mobility task (e.g., increase step height, step length or cadence).

The long-term goal of our research is to: 1) explain mobility task performance within the context of impaired module patterns, and 2) develop a clinical assessment tool

specific to post-stroke mobility that directly relates impaired function to impairment of specific module patterns in order to guide therapeutic interventions. As a first step towards this goal, the study in Chapter 3 was aimed at defining the underlying motor patterns that contribute to specific mobility tasks in healthy subjects (e.g., fastest comfortable walking (FC), high stepping (HS), long stepping (LS), quick stepping (QS)) in order to establish how a subject's ability to modify gait in response to changing task demands is reflected in module composition and timing. These specific mobility tasks were then investigated in subjects post-stroke and the module composition and timing, in addition to the ability to perform the mobility tasks, were compared to those measures found in healthy subjects. Specifically, we aimed to assess how deficits in mobility relate to motor control deficits in subjects post-stroke. It was expected that mobility task performance in post-stroke subjects would be higher in those subjects with a greater number of independent modules. Additionally, it was expected that mobility task performance in post-stroke subjects would be reflected in changes in module composition and/or timing. Thus, a limited ability to change module composition and/or timing would indicate limited mobility task performance.

Recent forward dynamic simulation studies have examined whether modules during non-impaired steady-state walking perform specific biomechanical functions such as body support, forward propulsion, leg swing and mediolateral balance control (Allen et al. 2012; Neptune et al. 2009). Because steady-state walking alone does not provide a full assessment of a subject's ability to perform a variety of mobility tasks, the goal of the study in Chapter 4 was to gain a more complete understanding of the functional role that each module contributes towards the performance of specific mobility tasks during healthy walking (e.g., quick stepping and high stepping). This was accomplished using 3D muscle-actuated forward dynamics simulations that characterize the contributions of

each module to the biomechanical subtasks of walking while healthy subjects performed high stepping and quick stepping mobility tasks. It was expected that the same number of modules that are required to produce healthy steady state walking would be able to produce high and quick stepping tasks. However, it was also expected that the modules in quick stepping and high stepping would have differences in timing during the gait cycle compared to healthy steady state walking. Because the primary experimental module modifications occurred to the timing peaks in swing and pre-swing (Chapter 3), it was expected that modules that include muscles crossing the hip joint (Modules 1 and 4), in addition to ankle dorsiflexors (Module 3), would have primary contributions to controlling the modifications to the swing phase of gait that occur in the quick and high stepping mobility tasks.

Chapter 2: The Influence of Locomotor Rehabilitation on Module Quality and Post-Stroke Hemiparetic Walking Performance[1]

INTRODUCTION

Stroke is the leading cause of long-term disability in the United States (Roger et al. 2012). Although the manifestations of disability post-stroke vary, several features of hemiparetic gait are common, including diminished speed, increased duration of stance on the non-paretic limb, increased duration of double support and asymmetric joint kinematics and kinetics (Higginson et al. 2006; Richards 1996). Because improved walking ability is central to rehabilitation of stroke patients (Dobkin 2005), assessments are needed to evaluate walking performance throughout the rehabilitation process. Previous assessments have compared self-selected walking speed (Bowden et al. 2008), propulsive and braking impulses (Bowden et al. 2006), paretic leg propulsion (Bowden et al. 2006), step length asymmetry (Allen et al. 2011; Balasubramanian et al. 2007), and pre-swing leg angle (Peterson et al. 2010). Since gait impairments are the result of deficient neuromuscular control, we have recently focused on quantifying the neuromuscular control deficits exhibited by individuals post-stroke. In healthy adults and persons post-stroke, it has been shown that the biomechanical subtasks of walking (e.g., body support, forward propulsion, leg swing and mediolateral balance control) are produced by co-activated muscles or modules (Allen et al. 2012; Neptune et al. 2009). In healthy adults these modules are activated independently. In contrast, individuals post-

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R.L.R. Determined quality measures, ran statistical analyses, and drafted the manuscript; D.J.C. Created pipeline for the determination of module number, compositions and timings; M.G.B. Collected experimental data; S.A.K. Oversaw the collection of the experimental data; R.R.N. Supervised data analysis; S.A.K. and R.R.N. Obtained funding for the project, assisted with data interpretation and methodological development; All authors discussed the results and interpretations and contributed to the manuscript at all stages.

stroke exhibit poor inter-muscular coordination characterized by co-activation (timing overlap) of modules that are independent in healthy individuals (Clark et al. 2010). Given that modules control the biomechanical subtasks of movement, this finding suggests the biomechanical subtasks of walking are interfering with one another. Greater interference between subtasks is expected to lead to poorer walking performance while less interference is expected to lead to better walking performance. Indeed, studies found a higher number of modules post-stroke was positively associated with better performance in various clinical and biomechanical assessments of walking, including walking speed, ability to change walking speed (increase from preferred to fast), Dynamic Gait Index, step length symmetry and propulsion symmetry (Bowden et al. 2010; Clark et al. 2010). Thus, improvements in modular organization during rehabilitation may lead to a more normal gait pattern and improved walking performance.

In healthy adults, analyses of the modular organization have revealed that well-coordinated walking can be produced by exciting four co-activation modules: Module 1 (hip and knee extensors) in early stance, Module 2 (ankle plantarflexors) in late stance, Module 3 (tibialis anterior and rectus femoris) during swing, and Module 4 (hamstrings) in late swing and early stance, with each module providing essential biomechanical functions (Neptune et al. 2009). Persons with post-stroke hemiparesis typically have fewer modules that are less organized than in healthy individuals (Clark et al. 2010). Even in those individuals who have four modules post-stroke, the modules differ in composition (i.e., the relative weighting of each muscle in each module) and timing (i.e., the activation of those modules over the gait cycle) from those of healthy individuals, which likely adversely affects their walking ability. Although it has been shown that independent activation of modules is important, it is also necessary to ensure that the quality of modules is appropriate with regard to timing and composition. Indeed,

individuals post-stroke who have an appropriate number of modules often exhibit walking deficits relative to healthy individuals (Clark et al. 2010). Therefore, improvement of the composition and timing of their modular organization such that it better matches the organization of healthy subjects could significantly improve locomotor performance.

However, whether locomotor therapy can improve module composition and timing and if these improvements lead to better walking performance is unclear (e.g., Den Otter et al. 2006). Therefore, the goal of this study was to examine the influence of a locomotor rehabilitation therapy on module composition and timing and walking performance in post-stroke hemiparetic subjects. Specifically, we assessed whether those subjects with four modules pre-therapy improved their post-therapy module composition and timing and walking performance. In addition, we compared module composition and timing post-therapy in all subjects with four modules post-therapy, grouped by pre-therapy number of independent modules, to determine whether the number of modules an individual had pre-therapy influences their post-therapy modular organization and biomechanical measures of gait performance. Specific measures of gait performance included self-selected walking speed, paretic step length asymmetry, paretic pre-swing leg angle and propulsion asymmetry.

METHODS

Participants

Study participants were a subset from a larger study on the effects of locomotor training post-stroke (Bowden et al. 2013). Twenty-seven post-stroke hemiparetic subjects participated in a 12-week, 36 session locomotor training program that included stepping

on a treadmill with body weight support and manual assistance (Bowden et al. 2013). The inclusion criteria were: stroke within 6 months to 5 years; hemiparesis secondary to a single unilateral stroke (Fugl-Meyer LE score <34); no significant lower extremity joint pain, range of motion limitations, or major sensory deficits; able to walk independently with an assistive device over ten meters on a level surface; able to walk on a daily basis in the home; no severe perceptual or cognitive deficits; no significant lower limb contractures; and no significant cardiovascular impairments contraindicative to walking. Data from a single walking session were acquired from 19 aged-matched healthy subjects. All subjects provided informed consent to an institutionally approved protocol.

Experimental set-up and procedure

Subjects performed 30-sec walking trials on a split-belt instrumented treadmill (Techmachine, Andrézieux Boutheon, France) at their self-selected speed both pre- and post-therapy. Practice trials were performed to ensure subjects were comfortable with the experimental setup. Subjects walked approximately 10-sec prior to each data collection to ensure they had reached a steady-state walking pattern. Reflective kinematic markers were placed on the limbs and torso using a modified Helen Hayes marker set. Marker locations were recorded in three dimensions at 100 Hz using a twelve-camera motion capture system (Vicon Motion Systems). A 16-channel EMG system (Konigsburg Instruments, Pasadena, CA) was used to record EMG data at 2000 Hz bilaterally from the tibialis anterior (TA), soleus (SO), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), lateral hamstrings (LH), and gluteus medius (GM). Bilateral 3D ground reaction forces (GRFs) were recorded at 2000 Hz.

Data analysis

Kinematic and kinetic data were processed using Visual3D (C-Motion, Inc., Germantown, MD). Kinematic and GRF data were low-pass filtered using a fourth order Butterworth filter with cutoff frequencies of 6 Hz and 20 Hz, respectively. EMG was high pass filtered with a cutoff frequency of 40 Hz, de-meaned, low pass filtered with a cutoff frequency of 10 Hz using a 4th order Butterworth filter and normalized to its peak values. Gait cycle time was determined from the GRF data. All data were time normalized to 100% of the gait cycle.

Biomechanical and EMG measures were analyzed using Matlab (The Mathworks, Natick, MA). Pre-swing leg angle was computed as the maximum angle between a line from the pelvis center-of-mass to the foot center-of-mass and vertical (positive when foot is posterior to the pelvis) during the double support phase (Peterson et al. 2010). Propulsion asymmetry was quantified as the proportion of total anterior GRF generated by the paretic leg subtracted from 0.5 and then taking the absolute value (Bowden et al. 2006). Paretic step ratio was calculated as the ratio of the paretic step length to the overall stride length (Balasubramanian et al. 2007). To compute step length asymmetry, this number was then subtracted from 0.5 and the absolute value of the difference was taken.

The number of modules required to account for >90% of the EMG variability was found using non-negative matrix factorization previously described in detail (Clark et al. 2010). To assess module quality, the module composition and timing for each post-stroke participant were compared to the average module composition and timing from the control group. Pearson's correlation coefficient was used to compare the composition of each module, represented by a 1x8 array of muscle weightings, between each stroke participant and the controls. Module composition quality was defined as the correlation coefficient, with 1.0 being a perfect association with the healthy group mean. The quality

of module timing was assessed by calculating a timing error, defined as the difference in timing peaks of the hemiparetic modules relative to the control group as a percentage of the gait cycle. In Module 3, where the module has two timing peaks, overall timing quality was calculated as the average of the two timing errors. To show variability in quality within the healthy subject group each healthy subject's module composition and timing were compared with the healthy group average such that their module composition and timing quality were not precisely 1.0 and 0.0 respectively.

Statistical analysis

All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC). For subjects with four modules pre- and post-therapy, self-selected speed, paretic step length asymmetry, paretic pre-swing leg angle, propulsion asymmetry, module timing quality and module composition quality were compared using paired t-tests. Using false discovery rate control to correct for multiple comparisons, additional t-tests were performed comparing the composition, timing and biomechanical measures for these subjects both pre- and post-therapy to the control subjects. For all subjects with four modules post-therapy, separate repeated measures ANOVAs (α=0.05) and post-hoc t-tests with a Bonferroni correction for multiple comparisons were used to compare 1) module timing, 2) module composition and 3) biomechanical measures for four groups: those persons with hemiparesis with 2, 3 and 4 modules pre-therapy, respectively, and the controls.

RESULTS

This study includes data for all subjects in the larger study who had four modules post-therapy (n=22). Characteristics of the subjects include the following: 14 left

hemiparesis; 15 men; age: 57.3 + 13.2 years; 19.0 + 13.0 months post-stroke; pre-therapy walking speed: 0.48 ± 0.20 m/s; pre-therapy lower extremity Fugl-Meyer: 22.9 ±4.4; and pre-therapy Dynamic Gait Index: 13.5 ± 3.2.

Subjects with four modules pre- and post-therapy

Nine of the 28 hemiparetic subjects had four modules both pre- and post-therapy. When comparing the module composition and timing quality of the four modules pre- and post-therapy, the only significant change was improved timing for the ankle plantarflexor module (Module 2; $p=0.0132$; Table 2.1). The average post-therapy timing peak of the plantarflexor module was more defined and occurred 8.45% of the gait cycle (Table 2.1) later in stance, which more closely resembled the control group (compare Figs. 1b and 1c to 1a). In these subjects, two walking performance measures also showed improvements post-therapy. Self-selected speed increased ($p=0.0114$) and pre-swing leg angle increased (i.e., was more extended, $p=0.0440$) following therapy. In addition, reduction of propulsion asymmetry post-therapy approached significance ($p=0.1121$).

Compared to the controls, plantarflexor timing was impaired pre-therapy ($p=0.0004$) and improved post-therapy such that t-tests with the control subjects no longer showed a significant difference ($p=0.65$; Table 2.2). The hip and knee extensor module timing was impaired pre-therapy (Module 1; $p=0.0132$), and marginally improved ($p=0.1121$) post-therapy. The tibialis anterior and rectus femoris module (Module 3) timing, plantarflexor module composition and hip and knee extensor module composition remained impaired both pre- and post-therapy. These subjects had diminished speed ($p<0.0001$) and leg angle ($p<0.0001$) as well as propulsion asymmetry ($p<0.0001$) and step length asymmetry ($p<0.0001$) pre-therapy as compared with control

subjects, and although most of these quantities improved post-therapy, they still remained impaired compared to the control subjects.

Table 2.1: Comparisons of module timing quality, module composition quality and biomechanical measures pre- and post-therapy (paired t-test results). Means ± standard deviations are listed for each measure for pre-therapy minus post-therapy as well as the post-therapy means ± standard deviations. Bold indicates rows that are significant or marginally significant.

Module Timing Quality

Module	p-value	Pre - Post	Post
1	0.6346	0.04 ± 0.17	0.10 ± 0.11
2	**0.0132**	0.08 ± 0.07	0.05 ± 0.05
3	0.1926	-0.14 ± 0.24	0.25 ± 0.15
4	0.3053	-0.02 ± 0.05	0.09 ± 0.08

Module Composition Quality

Module	p-value	Pre - Post	Post
1	0.2868	-0.11 ± 0.24	0.71 ± 0.19
2	0.6904	-0.05 ± 0.32	0.79 ± 0.26
3	0.6508	0.04 ± 0.18	0.82 ± 0.17
4	0.3021	-0.12 ± 0.26	0.82 ± 0.14

Biomechanical Measures

Measure	p-value	Pre - Post	Post
Speed	**0.0114**	-0.29 ± 0.14	0.78 ± 0.26
Leg Angle	**0.0440**	-5.83 ± 4.35	19.85 ± 6.07
Abs PP	**0.1121**	0.11 ± 0.11	0.15 ± 0.06
Abs PSR	0.6904	0.01 ± 0.08	0.05 ± 0.06

Table 2.2: Comparisons of module timing quality, module composition quality and biomechanical measures pre-therapy and post-therapy with controls. Means ± standard deviations are listed for each measure for pre-therapy as well as post-therapy. Bold indicates rows that are significant or marginally significant.

Module Timing Quality

Module	Pre	p-value	Post	p-value	Control
1	0.14 ± 0.14	**0.0132**	0.10 ± 0.11	0.1121	0.05 ± 0.06
2	0.14 ± 0.10	**0.0004**	0.05 ± 0.05	0.6508	0.04 ± 0.05
3	0.11 ± 0.15	**0.0349**	0.25 ± 0.15	**<0.0001**	0.04 ± 0.05
4	0.06 ± 0.07	0.3187	0.09 ± 0.08	0.0958	0.04 ± 0.06

Module Composition Quality

Module	Pre	p-value	Post	p-value	Control
1	0.60 ± 0.11	**0.1121**	0.71 ± 0.19	0.6904	0.75 ± 0.22
2	0.74 ± 0.17	**<0.0001**	0.79 ± 0.26	**0.0160**	0.94 ± 0.08
3	0.86 ± 0.10	0.6904	0.82 ± 0.17	0.7614	0.84 ± 0.13
4	0.70 ± 0.25	**<0.0001**	0.82 ± 0.14	**0.0052**	0.93 ± 0.06

Biomechanical Measures

Measure	Pre	p-value	Post	p-value	Control
Speed	0.46 ± 0.17	**<0.0001**	0.78 ± 0.26	**0.0057**	1.11 ± 0.22
Leg Angle	13.21 ± 3.59	**<0.0001**	19.85 ± 6.07	**0.0625**	23.20 ± 2.85
Abs PP	0.27 ± 0.17	**<0.0001**	0.15 ± 0.06	**<0.0001**	0.01 ± 0.01
Abs PSR	0.06 ± 0.04	**<0.0001**	0.05 ± 0.06	**<0.0001**	0.01 ± 0.01

All subjects with four modules post-therapy

Twenty-two subjects had four modules post-therapy. Of these, 11 subjects had three modules pre-therapy (five with merged Modules 1 and 4, two with merged Modules 1 and 2, and four with merged Modules 2 and 4) and two subjects had two modules pre-therapy, with only an independent Module 3. Because only two subjects had two modules pre-therapy, the corresponding results had low statistical power, and therefore fewer comparisons were significant. They are not discussed further, but are included in Table 2.3 for completeness.

The timing error for the ankle plantarflexor module (Module 2) for those subjects with three pre-therapy modules was significantly ($p<0.001$) higher compared to subjects that had four modules pre-therapy and from the control subjects (Table 2.3). The timing for subjects with three modules pre-therapy was less defined and had increased activity in early stance relative to the control subjects and those subjects with four modules pre-therapy (compare Figs. 2.1d to 2.1c and 2.1a). There was also a significant difference in the composition of Module 2 in those subjects who had three modules pre-therapy as compared with the control subjects (Table 2.3). There was a diminished contribution from the soleus muscle in Module 2 in these subjects (compare Fig. 2.1d and 2.1a). In addition, both the timing and composition of Module 4 (hamstrings) in subjects who had three modules pre-therapy were significantly different from that of the control subjects. These modular organization differences were accompanied by an increased step length and propulsion asymmetry, slower self-selected speed and decreased pre-swing leg angle (Table 2.3; $p<0.05$) in subjects who had three modules pre-therapy relative to those who had four modules pre-therapy and the control subjects.

Table 2.3: Comparisons of module timing quality, module composition quality and biomechanical measures at post-therapy depending on the number of modules pre-therapy (ANOVA results). Means ± standard deviations are listed for each measure for each pre-therapy number of module grouping. Each pre-therapy number of module grouping is colored as is the marker indicating statistical significance. Red indicates the subjects who had two modules pre-therapy. Orange indicates subjects who had three modules pre-therapy. Green indicates subjects who had four modules pre-therapy. Purple indicates control subjects. This data is graphically depicted in Figure 2.2.

Module Timing Quality

Module	ANOVA p-value	Pre - 2	Pre - 3	Pre - 4	Control
1	0.0813	0.09 ± 0.09	0.12 ± 0.12	0.10 ± 0.11	0.05 ± 0.06
2	< 0.0001	0.10 ± 0.06	0.20 ± 0.17**	0.05 ± 0.05*	0.04 ± 0.05*
3	< 0.0001	0.46 ± 0.04***	0.12 ± 0.09***	0.25 ± 0.15***	0.04 ± 0.05***
4	0.0002	0.23 ± 0.11*	0.13 ± 0.08*	0.09 ± 0.08	0.04 ± 0.06**

Module Composition Quality

Module	ANOVA p-value	Pre - 2	Pre - 3	Pre - 4	Control
1	0.0635	0.40 ± 0.03	0.58 ± 0.29	0.71 ± 0.19	0.75 ± 0.22
2	< 0.0001	0.40 ± 0.12**†	0.73 ± 0.25*†	0.79 ± 0.26*	0.94 ± 0.08**
3	0.3244	0.65 ± 0.13	0.80 ± 0.17	0.82 ± 0.17	0.84 ± 0.13
4	<0.0001	0.37 ± 0.09**	0.64 ± 0.35*	0.82 ± 0.14*	0.93 ± 0.06**

BioMechanical Measures

Module	ANOVA p-value	Pre - 2	Pre - 3	Pre - 4	Control
Speed	< 0.0001	0.63 ± 0.13*	0.55 ± 0.25*	0.78 ± 0.26*	1.11 ± 0.22***
Leg Angle	< 0.0001	16.70 ± 3.59	13.61 ± 7.52*†	19.85 ± 6.07†	23.20 ± 2.85*
Abs PP	< 0.0001	0.12 ± 0.09	0.25 ± 0.16*	0.15 ± 0.06*	0.01 ± 0.01**
Abs PSR	0.0003	0.02 ± 0.02	0.12 ± 0.16*	0.05 ± 0.06	0.01 ± 0.01*

** indicates statistical significance for the difference in means using Bonferrroni t-tests

†† indicates marginal significance using Bonferroni t-tests

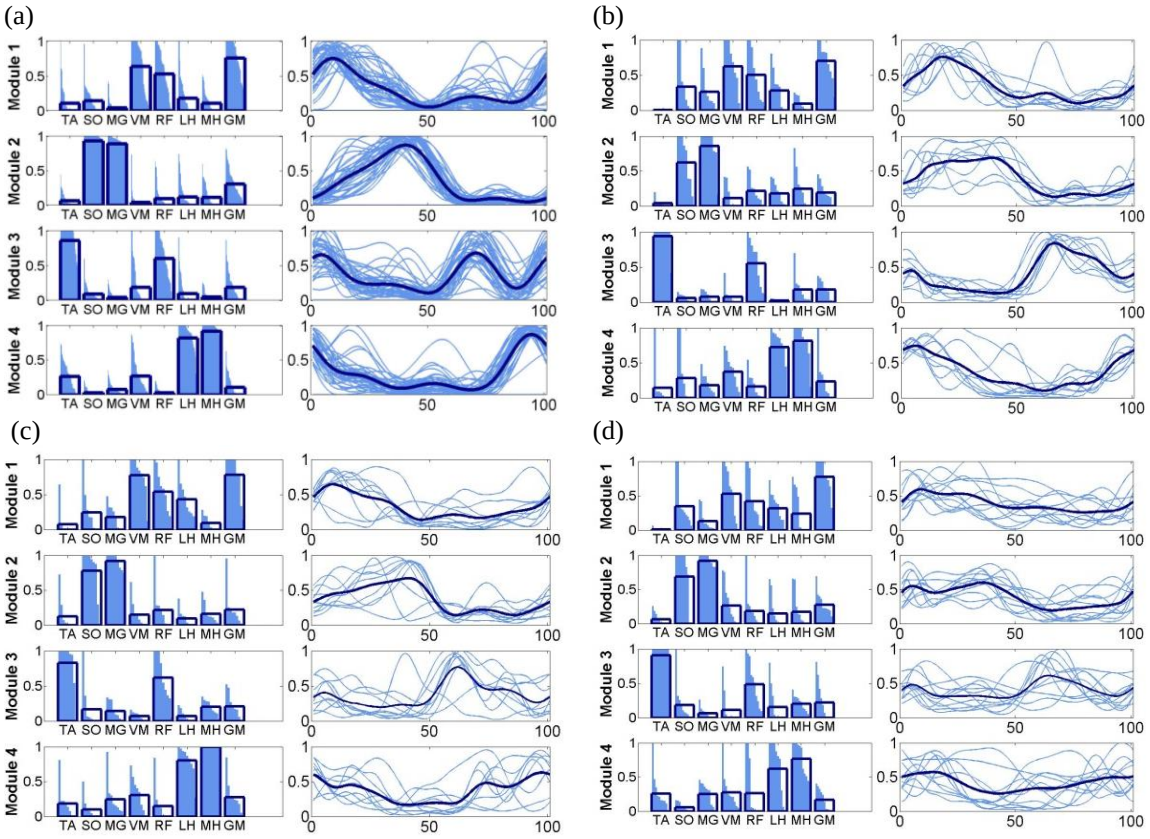

Figure 2.1: Module composition (left, bar plots), the relative contribution of the muscles to each module, and activation timing (right, line plots) of that module. Individual subject (lighter histograms and lines) and group average (bold bar outlines and darker lines) data are shown for: (a) Control Subjects, (b) Pre-Therapy for subjects with 4 modules Pre-Therapy (c) Post-Therapy for subjects with 4 modules Pre-Therapy (d) Post-Therapy for subjects with 3 modules Pre-Therapy. Abbreviations: TA, tibialis anterior; SO, soleus; MG, medial gastrocnemius; VM, vastus medialis; RF, rectus femoris; LH, lateral hamstrings; MH, medial hamstrings; GM, gluteus medius.

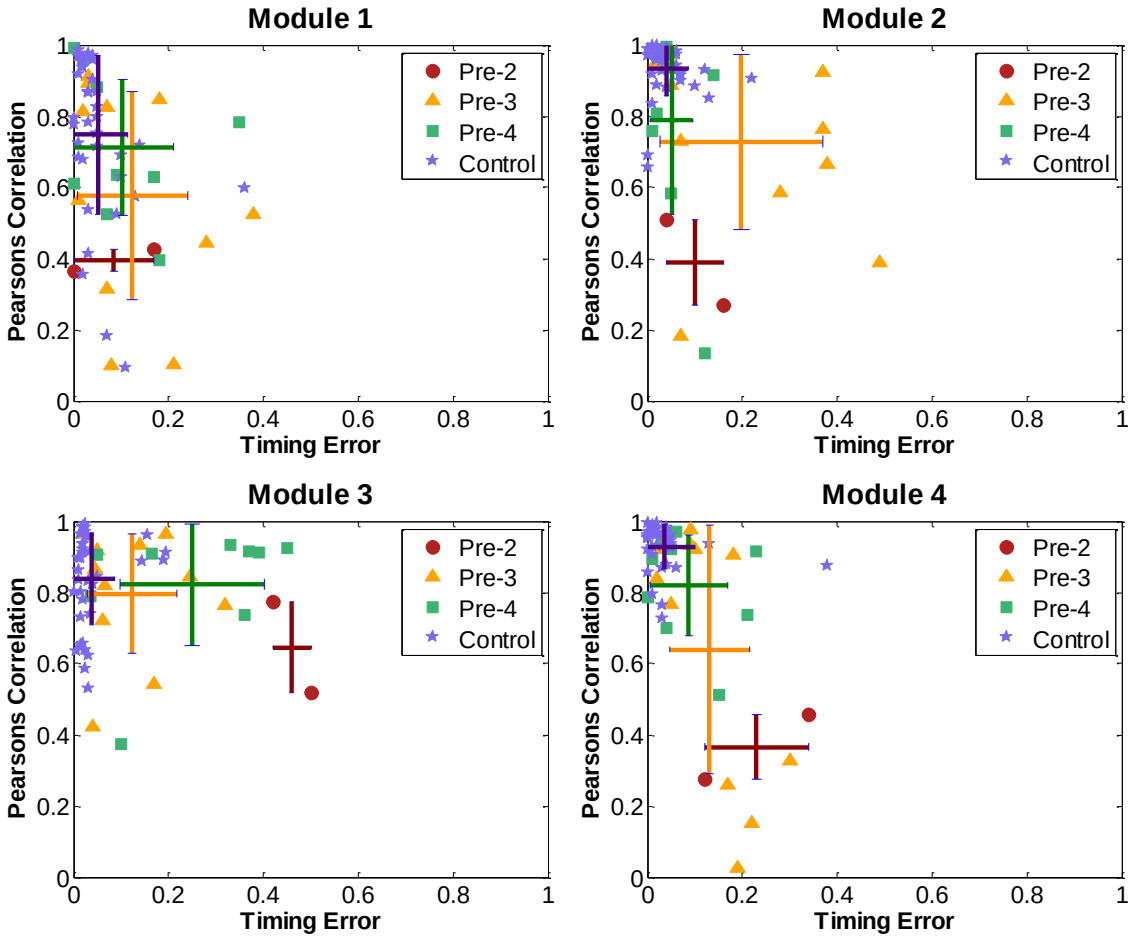

Figure 2.2: Timing error and Pearson's correlation are plotted for each subject. Means ± standard deviations are shown with error bars for each measure for each pre-therapy number of modules. Each pre-therapy number of modules is colored: Red circles indicate the subjects who had two modules pre-therapy; Orange triangles indicate subjects who had three modules pre-therapy; Green squares indicate subjects who had four modules pre-therapy; Purple stars indicate control subjects.

DISCUSSION

The goal of this study was to examine the influence of a locomotor rehabilitation therapy on the quality of module composition and timing and post-stroke hemiparetic walking performance. Overall, we found that manual body-weight supported treadmill training does influence some aspects of module composition and timing quality that leads to improvements in symmetry and speed depending on pre-therapy modular organization.

Hemiparetic plantarflexor impairment

Plantarflexor impairment is commonly observed in hemiparetic walking. In both control and hemiparetic subjects, the soleus is an important contributor to forward propulsion during pre-swing and is critical to increasing walking speed (Hall et al. 2011). In this study, impaired plantarflexor activity was exhibited by both reduced participation in Module 2 (subjects with three modules pre-therapy) and impaired timing (subjects with three modules pre-therapy and pre- to post-therapy four module comparison). Compared to control subjects, paretic leg ankle plantarflexor muscle activity has been shown to be reduced in hemiparetic subjects (Higginson et al. 2006; Peterson et al. 2010), which leads to diminished body propulsion and leg swing initiation (Peterson et al. 2010).

Improved timing of plantarflexor module

An important finding of this study was that gait recovery post-stroke can be associated with temporal changes in motor modules. The locomotor therapy improved the timing of Module 2 (plantarflexors) in those subjects who had four modules prior to therapy. This improvement was accompanied by an increased speed and pre-swing leg angle (i.e., the leg was more extended prior to toe-off). Also, greater propulsion symmetry following therapy approached significance. Improvements in these performance measures were likely due to the better timing of the plantarflexor module

since the plantarflexors are essential for body propulsion (McGowan et al. 2008; Neptune et al. 2001; Neptune et al. 2008). Another important finding was that locomotor training leads to an increased leg angle in late stance, which is a more effective kinematic position for the plantarflexor force to propel the body forward (Peterson et al. 2010). This is important for gait speed and also for step length symmetry (Peterson et al. 2010). We believe that improvement in plantarflexor timing is likely the largest contributor to the improvements in the biomechanical measures. However, it is likely that the therapy also produced benefits in additional domains beyond muscle coordination (e.g., strength/power, endurance, balance and confidence) that contributed to improved walking performance and also correlate with improved biomechanical measures.

The important finding of improved plantarflexor module timing is in contrast with den Otter et al. (2006), which suggested gait recovery is not associated with temporal changes in individual muscle activity post-stroke. However, differences between studies are likely due to the variations in the actual rehabilitative therapies, and approaches for determining changes in timing, with our study determining peak amplitude and the previous study looking at periods of activation over the gait cycle. In addition, the previous study (Den Otter et al. 2006) only examined four muscles bilaterally (RF, BF, MG, and TA) and did not include the soleus. Including the soleus is important since previous modular analyses have suggested that improving soleus output during rehabilitation may provide the greatest improvement in walking performance (McGowan et al. 2009).

Pre-therapy module number influences response to therapy

Relative to those with fewer than four modules pre-therapy, individuals with four modules pre-therapy had better walking performance, modular composition and module

timing both pre and post-therapy. In those subjects who had three modules pre-therapy, Module 2 timing post-therapy was worse than subjects who had four modules pre-therapy. These subjects also had poor timing and composition compared to control subjects. This is due to pre-therapy merging of non-impaired modules (Clark et al. 2010). Only five of the eleven subjects with three modules pre-therapy and four modules post-therapy had an independent plantarflexor module pre-therapy. Although these subjects gained an independent plantarflexor module post-therapy, this module still had impaired timing. Hemiparetic gait is commonly associated with temporal abnormalities in the gait cycle, including over-activity of the plantarflexor muscles during early stance (Den Otter et al. 2007; Higginson et al. 2006). Although early stance soleus activity may contribute to stability, by reducing knee flexion in response to early stance loading (Higginson et al. 2006) this soleus activity leads to increased braking (i.e. posterior GRF) in early stance.

We also found subjects who had four modules pre-therapy (n=8) did not have significant Module 4 (hamstrings) timing error. However, subjects with three modules pre-therapy (n=11, only two of whom had an independent hamstrings module pre-therapy) did have significant timing error in Module 4 post-therapy. The latter results are consistent with abnormalities in temporal patterning of the hamstrings as commonly seen in post-stroke hemiparetic walking, especially regarding co-activation of the hamstrings and rectus femoris similar to merging Modules 1 and 4 in subjects with three modules (Den Otter et al. 2007). The hamstrings module accelerates the leg into swing in early stance and decelerates the leg in late swing in preparation for foot contact (Neptune et al. 2009). Thus, prolonged hamstring activity may interfere with propulsion generation (Neptune et al. 2011), which is consistent with our finding of asymmetrical paretic propulsion in these subjects compared to the control subjects.

Methodological considerations

A potential limitation of this study is that due to recording EMG from a smaller set of muscles, we were only able to identify four modules. Recent simulation (Allen et al. 2012; Neptune et al. 2009) and experimental (Ivanenko et al. 2004) studies analyzing a greater number of muscles have found that 5-6 modules are necessary to control walking in healthy subjects, with the fifth module containing large contributions from the erector spinae and iliopsoas muscles. However, in this study, EMG data from the same set of muscles was analyzed in the hemiparetic and control subjects to allow a direct comparison between groups. Future studies will endeavor to incorporate data from a larger number of muscles and modules.

CONCLUSION

In subjects with four modules pre- and post-therapy, a manual body-weight supported treadmill training program resulted in improved timing of the ankle plantarflexor module and a more extended paretic leg angle that allowed the hemiparetic subjects to walk faster and with more symmetrical (i.e., greater paretic leg) propulsion. Most subjects with three modules pre-therapy increased their number of modules and improved walking performance post-therapy, although they still had poorer walking performance than those that started with four modules. Thus, manual body-weight supported treadmill training has the potential to influence module composition and timing quality, which can lead to improvements in symmetry and speed depending on pre-therapy modular organization. These results provide rationale for selecting rehabilitation strategies that target specific aspects of modular organization depending on pre-therapy organization.

Chapter 3: Modular organization across changing task demands in healthy and post-stroke gait[2]

INTRODUCTION

In healthy adults, the biomechanical subtasks of steady state walking (e.g., body support, forward propulsion, leg swing and mediolateral balance control) have been shown to be generated by independent groups of co-excited muscles or modules (Allen et al. 2012; Neptune et al. 2009). However, individuals post-stroke display poor inter-muscular coordination characterized by a merging of modules that are normally independent in healthy individuals (Clark et al. 2010). A higher number of independent modules post-stroke has been associated with improved performance in various clinical and biomechanical assessments of walking, including increased walking speed, improved ability to increase walking speed (range from self-selected to fast), improved Dynamic Gait Index, and improved step length and propulsion symmetry (Bowden et al. 2010; Clark et al. 2010). Modules have also been shown to be associated with specific biomechanical functions during movement (Allen et al. 2012; Neptune et al. 2009), and the merging of modules interferes with the successful execution of the biomechanical functions (Allen et al. 2013). As more modules are merged, greater interference between subtasks occurs, leading to poorer walking performance. However, in a recent study we found that improvements in the number and quality of modules post-stroke with a clinical intervention resulted in improvements in walking ability (Chapter 2).

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[2] Significant portions of this chapter have been previously published as: Routson RL, Kautz SA, and Neptune RR. Modular organization across changing task demands in healthy and post-stroke gait. *Physiological Reports* 2: 1-14, 2014.
R.L.R. Analyzed and interpreted data and drafted manuscript; S.A.K. Oversaw the collection of the experimental data; R.R.N. Supervised data analysis; S.A.K. and R.R.N. Obtained funding for the project, assisted with data interpretation and methodological development; All authors discussed the results and interpretations and contributed to the manuscript at all stages.

In addition to steady state walking, daily lower limb mobility is comprised of many diverse motor tasks such as accelerating, stopping, turning and avoiding obstacles. Studies investigating healthy individuals executing tasks such as kicking a ball while walking (Ivanenko et al. 2005), running (Cappellini et al. 2006), walking with induced slipping (Oliveira et al. 2012), and running with cutting maneuvers (Oliveira et al. 2013), have identified module patterns similar to those in walking. Some of these studies also revealed adaptability in module timing (Cappellini et al. 2006; Oliveira et al. 2013) or changes in the number of modules (Ivanenko et al. 2005) in response to changing task demands. A recent study hypothesized that the central nervous system adapts the existing module structure to task demands rather than introducing new modules (Oliveira et al. 2012). Because each module contributes to specific biomechanical functions in healthy walking (Allen et al. 2012; Neptune et al. 2009), we expect that mobility tasks that require changes in specific biomechanical functions will affect the corresponding module patterns and timings associated with that function. Thus, a lack of independent modules or a lack of ability to change the timing of a specific independent module as is commonly seen in subjects post-stroke could affect a subject's ability to execute specific mobility tasks (e.g., increase step height, step length or cadence).

Our long-term goal is to: 1) explain mobility task performance within the context of impaired module patterns and 2) develop a clinical assessment tool specific to post-stroke mobility that directly relates impaired function to impairment of specific module patterns in order to guide therapeutic interventions. This would ultimately characterize an individual's overall mobility capability rather than typical mobility performance (i.e., what subjects can do versus how subjects typically perform). As a first step towards this goal, we will define the underlying motor patterns that contribute to specific mobility tasks in healthy subjects (e.g., fastest comfortable walking (FC), high stepping (HS), long

stepping (LS), quick stepping (QS)) in order to establish how a subject's ability to modify gait in response to specific changes in task demands is reflected in module composition and timing. We then will investigate these mobility capability tasks in subjects post-stroke by comparing the module composition, module timing and mobility capability performance of the post-stroke and neurologically healthy subjects. Since gait impairments are the result of deficient neuromuscular control, rather than assessing kinematics alone, this study aimed to quantify the neuromuscular control deficits exhibited by individuals post-stroke by assessing ability to modify module composition and/or timing. Achieving this will facilitate the assessment of how specific deficits in mobility capability relate to motor control deficits in subjects post-stroke, and thus enable clinical interventions guided by patient- and task-specific mobility goals.

METHODS

Experimental set-up and procedure

Kinematic, kinetic and electromyography (EMG) data were collected from 27 post-stroke subjects (Table 3.1) with hemiparesis secondary to a single unilateral stroke. Subject inclusion criteria consisted of the following: free of significant lower extremity joint pain, range of motion limitations, and major sensory deficits; able to ambulate independently with an assistive device over ten meters on a level surface; walk on a daily basis in the home; with no severe perceptual or cognitive deficits; free of significant lower limb contractures; and no significant cardiovascular impairments contraindicative to walking. Data were also collected from 17 healthy control subjects (Table 3.1) free from neurological disease and lower limb orthopedic impairments. All participants

provided written informed consent and the Institutional Review Board approved the protocol.

Each subject walked on a split-belt instrumented treadmill (Bertec, Columbus, Ohio) at their self-selected (SS) walking speed for 30 second trials in addition to a randomized block design of four steady state mobility capability tasks: walking at maximum speed (FC), and walking at self-selected speed with maximum cadence (QS), maximum step length (LS) and maximum step height (HS). Practice trials were performed to ensure subjects were comfortable with the experimental setup. To ensure that a steady-state walking pattern was achieved for the data collection, subjects walked approximately 10 seconds prior to data collection. For each of the mobility tasks, three trials were collected and the most successful (e.g., highest cadence) trial compared to the self-selected walking trial was used for data analysis. Mobility performance measures of task capability were speed change, cadence change, step length change and step height change, all with respect to the self-selected walking trial.

Table 3.1: Subject demographics. All post-stroke subjects were at least 6 months post-stroke.

Variable	Averages	SD	Range
Post-stroke group (n = 27)			
Age	60.15	12.08	28 - 76
OG self-select walking speed (m/s)	0.73	0.32	0.29 – 1.23
Berg Balance Score	47.70	6.79	25 - 55
Fugl-Meyer Assessment	22.85	6.95	9 - 34
Fugl-Meyer Assessment - Synergy	15.22	5.15	5 - 22
Sex (male/female)	18/9		
Control group (n = 17)			
Age	54.18	8.33	40 - 74
OG self-select walking speed (m/s)	1.20	0.19	0.75 – 1.46
Sex (male/female)	9/8		

Data collection and processing

Reflective kinematic markers were placed on the limbs and torso using a modified Helen Hayes marker set. Marker locations were recorded at 120 Hz using a twelve-camera motion capture system (PhaseSpace, Inc., San Leandro, CA) and GRF data were sampled at 2000 Hz. Kinematic and GRF data were filtered using a fourth-order Savitzky-Golay (Savitzky et al. 1964) least-square polynomial smoothing filter and were resampled at 100 Hz.

EMG was collected ((Motion Lab Systems, Inc., Baton Rouge, LA) bilaterally from the tibialis anterior (TA), soleus (SO), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), lateral hamstrings (LH) and gluteus medius (GM) at 1000 Hz. EMG data were high-pass filtered with a zero-lag fourth-order Butterworth filter (40Hz), demeaned, rectified and then low-pass filtered with a zero-lag fourth-order Butterworth filter (4 Hz). To focus on temporal dissimilarities in EMG, the EMG for each muscle was normalized to its peak value during each trial. In addition, EMG was time normalized to 100 percent of the gait cycle. The number of modules required to account for greater than 90 percent of the EMG variability accounted for (VAF) in each of the muscles was found using non-negative matrix factorization as previously described in detail (Clark et al. 2010). For each subject, modules were identified for each mobility task separately and then an ANOVA was performed comparing the number of modules for *all* subjects across all conditions.

Statistical analysis

All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC). After the modules were calculated for each task for each subject, in order to create a direct comparison across tasks the self-selected number of modules was used when comparing each mobility capability task to the self-selected condition.

Pearson's correlation coefficient was used to compare the composition of each module to the average module in SS walking (Oliveira et al. 2013; Chapter 2). To enable a one-to-one comparison to control subjects, post-stroke subjects with four modules were correlated with control subjects. Modules in all other subject groups were correlated to their own group average SS walking data (e.g., post-stroke subjects who had three modules were correlated with average SS walking data for the subjects with three modules). Higher correlations specify more similarity in module compositions. For each of the four groups of subjects (hemiparetic subjects with 2, 3 and 4 modules and healthy subjects) separate one-way ANOVAs ($p<0.05$) and post-hoc t-tests with Bonferroni corrections were used to compare the correlations across the mobility capability tasks.

To assess the differences in module timing each module's activation timing was integrated over 100 percent of the gait cycle and then the percentage of the total integrated module activation timing was calculated for six regions of the gait cycle (Figure 3.1) (Nott et al. 2014). For each of the four groups of subjects separate one-way ANOVAs ($p<0.05$) and post-hoc t-tests with Bonferroni corrections were used to compare the percentage of the total integrated module activation timing for each of the six regions of the gait cycle across the mobility capability tasks.

In addition, one-way ANOVAs ($p<0.05$) and post-hoc t-tests with Bonferroni corrections were used to compare the mobility capability performance measures (i.e., change in speed, cadence, step length and step height) across the four subject groups.

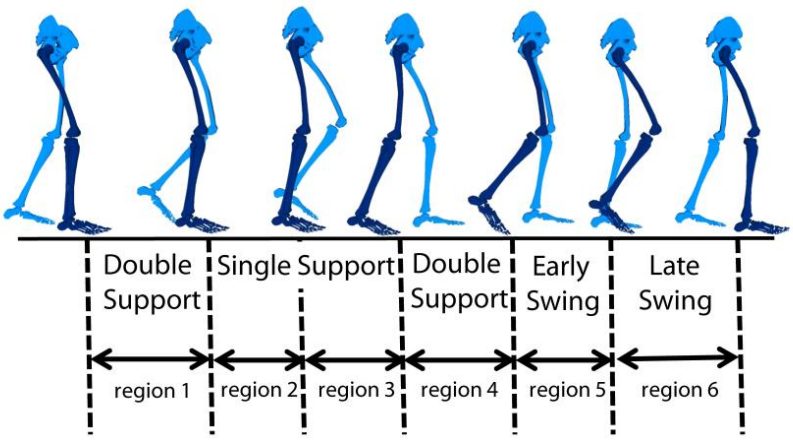

Figure 3.1: Region definitions over the gait cycle.

RESULTS

Control subjects

Four modules were necessary to reconstruct the EMG (e.g., Figure 3.2) collected in the majority of the control subjects in all mobility tasks (3.9 ± 0.5 SS; 3.9 ± 0.4 fastest comfortable walking (FC); 3.9 ± 0.3 quick stepping (QS); 3.9 ± 0.6 high stepping (HS); 3.5 ± 0.8 long stepping (LS)) with total VAF exceeding 0.98 for all tasks (0.99 ± 0.01 SS; 0.98 ± 0.01 FC; 0.98 ± 0.01 QS; 0.99 ± 0.00 HS; 0.99 ± 0.01 LS). Therefore, similar to what was previously performed to characterize healthy subject SS walking (Clark et al. 2010), typical healthy module composition and timing in all of the mobility tasks was extracted using four modules from each of the healthy subjects regardless of the number of modules assigned using the 90 percent of VAF criteria. In the current study, the modules observed in the control subjects for all of the mobility capability tasks were consistent with control modules previously found using the same number of muscles

(Figure 3.3) (Clark et al. 2010; Chapter 2) and quantitatively similar to previous studies that recorded from a larger set of muscles (Cappellini et al. 2006; Ivanenko et al. 2004). Module 1 is composed of hip and knee extensors, Module 2 is primarily composed of the plantarflexors, Module 3 is primarily composed of the tibialis anterior and rectus femoris, and Module 4 is composed of the hamstrings.

Module compositions were found to be consistent across tasks (Figure 3.4). While there was a statistically significant difference in module composition in Module 4 ($p=0.014$) which post-hoc Bonferroni t-tests revealed was between LS and QS mobility tasks, this difference appears relatively minor. All of the composition correlations to the average compositions of the SS walking data were greater than 0.65, showing a high similarity of all the module compositions during the mobility tasks to the SS condition.

However, there were clear differences in timing. The percentage of the Module 1 activation over the regions of the gait cycle (see Figure 3.1) varied in FC, QS and HS when compared to SS, with higher activation in Region 6 (late swing) in FC and QS and lower activation in Region 1 (early stance) in HS than in SS walking (Figure 3.4). Additionally, Module 2 activation varied in mid-stance in FC and QS when compared to SS walking with higher activation in Region 3 in FC and Region 2 in QS than in SS walking. Module 3 activation varied in QS and HS when compared to SS walking. In Module 3 in HS there was a higher activation in Region 6 (late swing) and lower activation in Region 4 (pre-swing) compared with SS walking, consistent with the prolonged activation throughout swing seen in Figure 3.3. Also, in Module 3, there was a higher activation in Region 4 (pre-swing) in QS compared with SS walking. The percentage of the Module 4 activation over the gait cycle varied in QS, HS and LS when compared to SS walking. There was more Module 4 activity in Region 5 (early swing) during QS than in SS walking. There was more Module 4 activity in Regions 4 and 5

(pre-swing and early swing) and less in 1 and 6 (late swing and early stance) in HS walking than in SS walking. Also, in LS walking there was a more uniform distribution of activation of Module 4 throughout the gait cycle with higher activation in Regions 2 and 4 and lower activation in Region 6 than in SS walking.

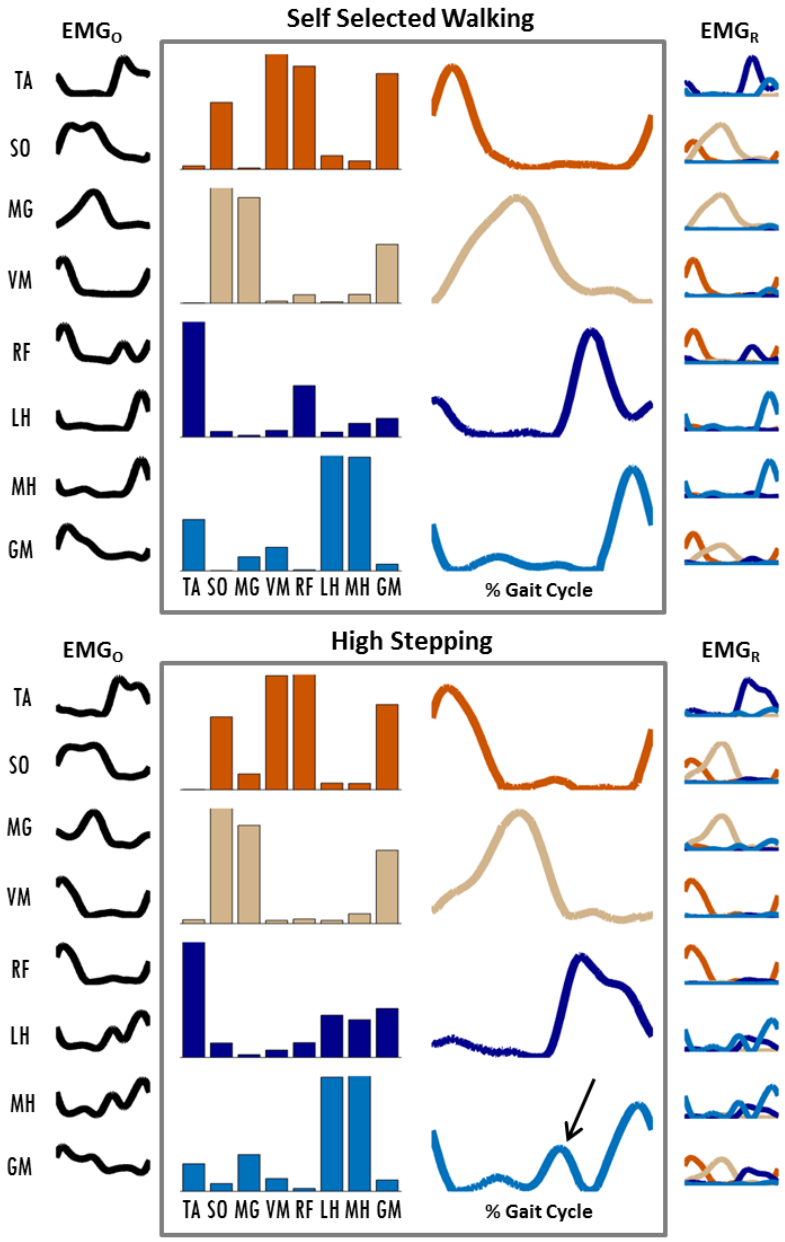

Figure 3.2: Processed EMG (*EMGO*), module composition matrices (bar plots), module activation timing, and reconstructed EMG (*EMGR*) for a representative control subject. The top plots depict data for SS walking and the bottom plots depict data for HS walking. The arrow points to the additional peak in Module 4 timing activation seen in HS walking. Orange is Module 1, beige is Module 2, dark blue is Module 3, and medium blue is Module 4. The components of each muscle's *EMGR* due to each module are colored the module colors respectively.

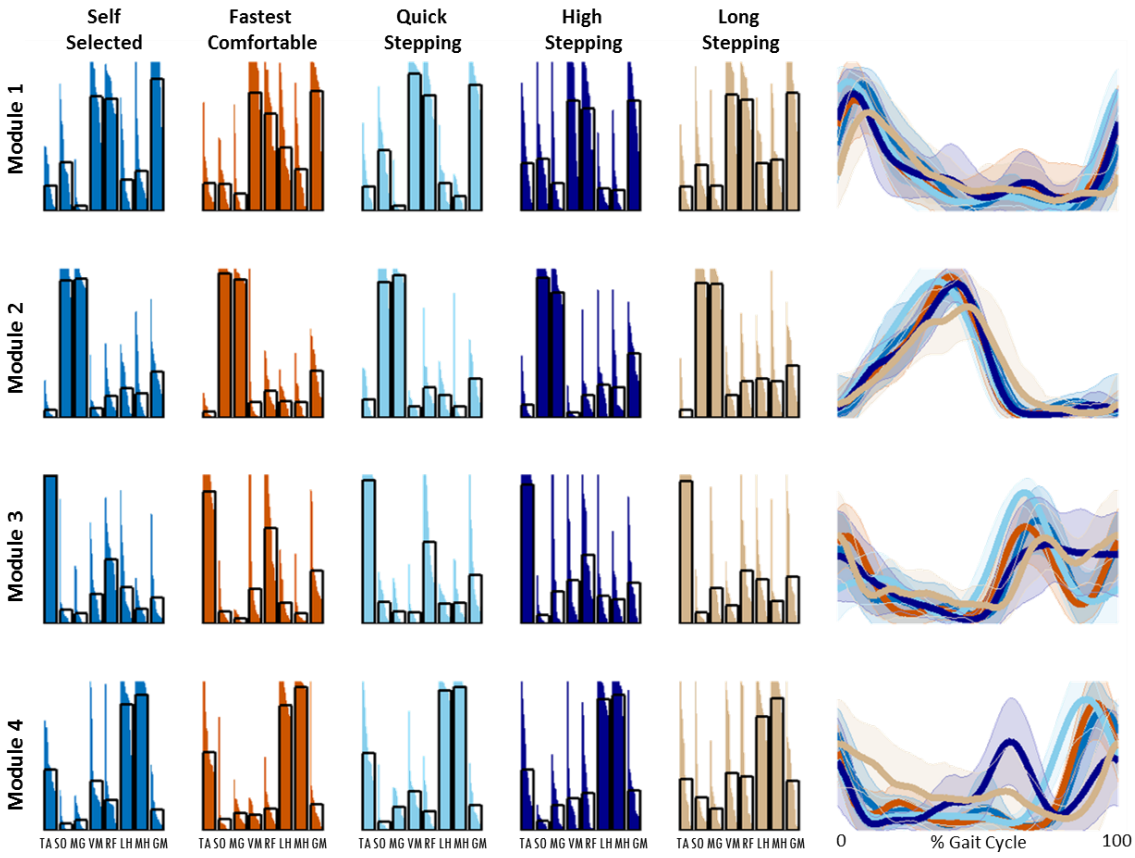

Figure 3.3: Average control subject modules for self-selected walking (medium blue), fastest comfortable walking (orange), quick stepping (light blue), high stepping (dark blue), and long stepping (beige). Module compositions are on the left (black boxes show average composition) and timing of the correspondingly colored module are on the right (bold lines show average and shaded areas show standard deviation). Module 1 is the top row, Module 2 is the second row, Module 3 is the third row, and Module 4 is the bottom row.

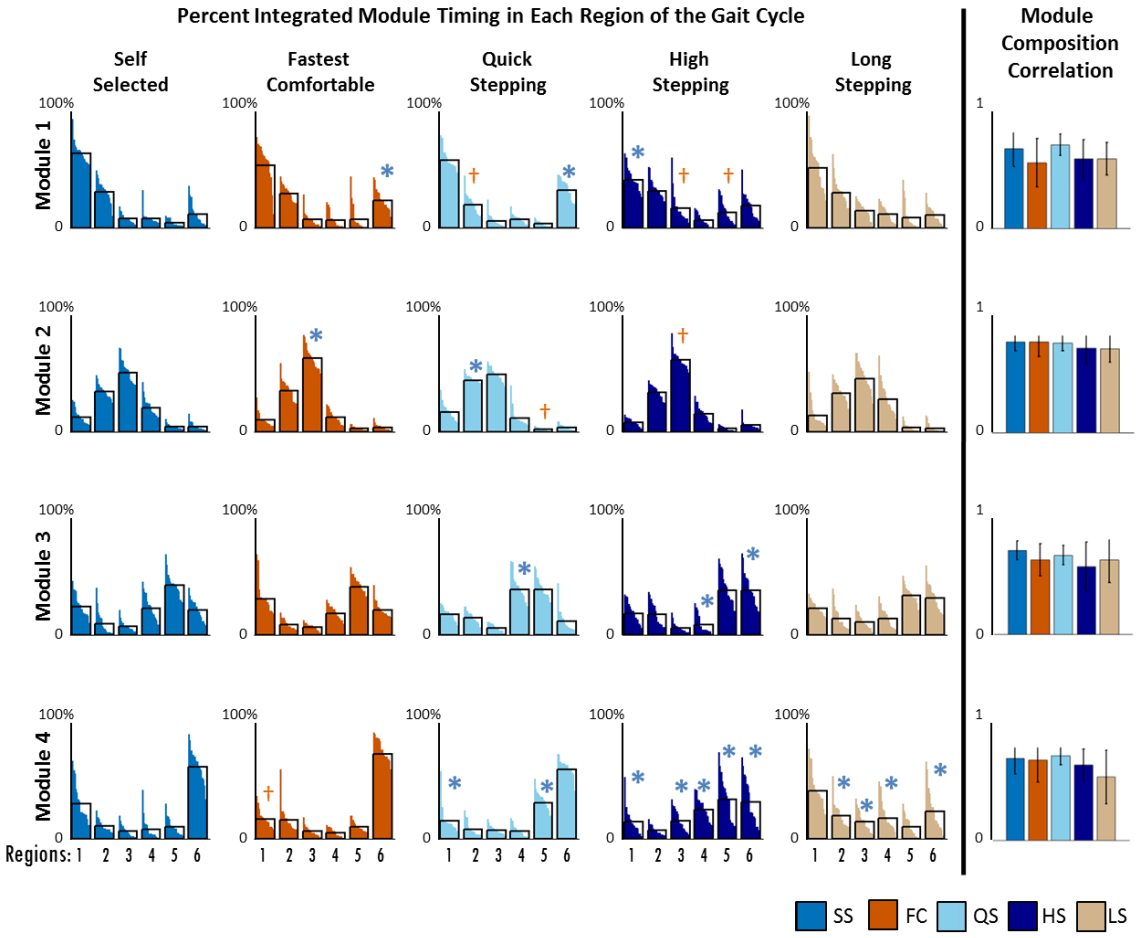

Figure 3.4: The first five bar graphs on the left represent the percent of total integrated module timing curve in each region of the gait cycle (Figure 3.1) for control subjects. ANOVAs were run for each module and region of the gait cycle across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) and "†" shows marginal significance ($\alpha<0.1$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only. The last column shows Pearson's correlations of module composition of control subjects to average module composition of control subjects. ANOVAs were run for each module across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only.

Post-Stroke subjects

A group analysis of *all* subjects (post-stroke and control) across mobility tasks revealed no significant difference between the number of modules for any of the tasks (one-way ANOVA; $p=0.78$). Of the 27 post-stroke subjects 6 had two modules, 15 had three modules, and 6 had four modules in the steady state walking condition.

Post-stroke subjects with four modules

The module compositions found in the four-module post-stroke subjects were similar to those of the control subjects (compare Figure 3.5 to Figure 3.3) such that the correlation with the average control modules was always greater than 0.6 (Figure 3.6). For the post-stroke subjects with four modules, each module's composition did not differ between mobility capability tasks.

Module timings in the post-stroke subjects with four modules were similar to the control subjects (Figure 3.5). Despite some visual differences in the average curves between mobility tasks, the percent of integrated module timing in the six regions of the gait cycle were not significantly different between any of the tasks (Figure 3.6). Specifically, the average timing curve of Module 4 did have two peaks during HS as it did for the control subjects (Figure 3.5, last column – note similar shape as in Figure 3.3), but there was a larger standard deviation post-stroke than in the control subjects. Indeed, Module 4 in Region 5 (early swing; $p=0.02$) had significantly ($\alpha<0.05$ for post-hoc t-tests) less activity in LS than QS and HS, and marginally less ($\alpha=0.0665$ for post-hoc t-tests) activity in SS than QS and HS. Additionally, the average timing curve of Module 4 peaked late in swing during LS as it did for the control subjects (compare Figures 3.3 and 3.5), although there was no significant differences between LS and SS walking.

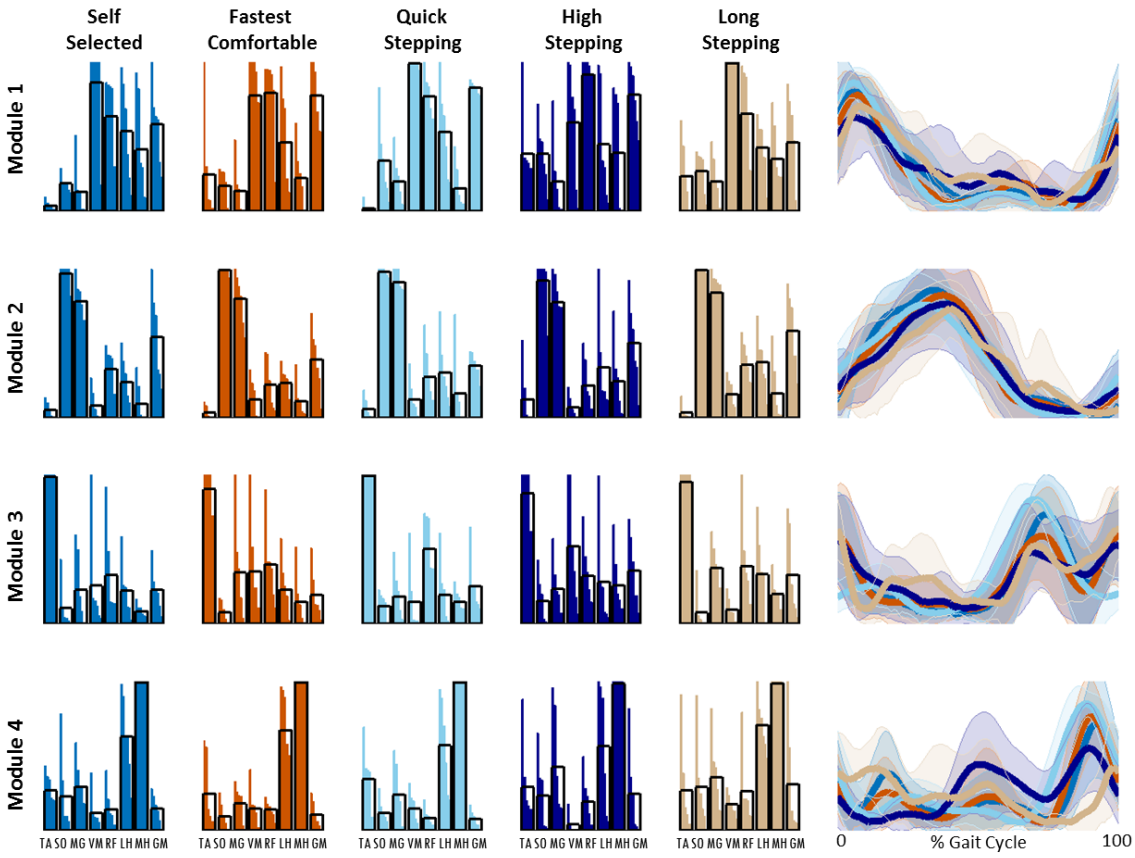

Figure 3.5: Average post-stroke subject modules for subjects with four modules are shown for all tasks. Module compositions are on the left and timing of the correspondingly colored module are on the right.

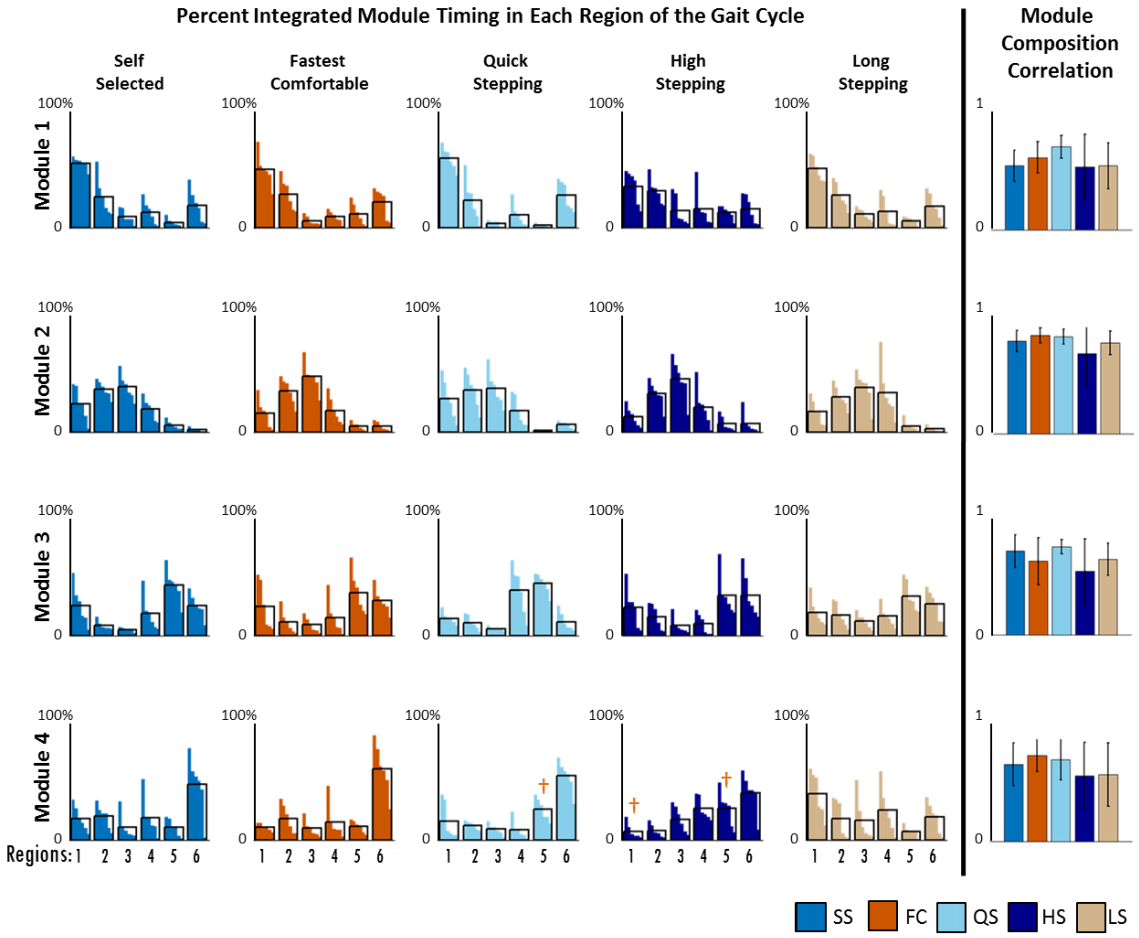

Figure 3.6: The first five bar graphs on the left represent the percent of total integrated module timing curve in each region of the gait cycle (Figure 3.1) for post-stroke subjects with four modules (n=6). ANOVAs were run for each module and region of the gait cycle across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) and "†" shows marginal significance ($\alpha<0.1$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only. The last column shows Pearson's correlations of module composition of post-stroke subjects with 4 modules to average module composition of control subjects. ANOVAs were run for each module across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only.

Post-stroke subjects with less than four modules

Post-stroke subjects with less than four modules also maintained consistency in their composition across the mobility tasks (Figures 3.7-3.10). Module timing was also not significantly different for any of the subjects with three modules across the mobility capability tasks. Module timing did change during LS for subjects with two modules (Figure 3.10) with a decreased activation of their Module 1 during mid-stance (Regions 2 and 3) compared to SS walking. All of the other tasks in subjects with two modules had similar timing profiles to one another.

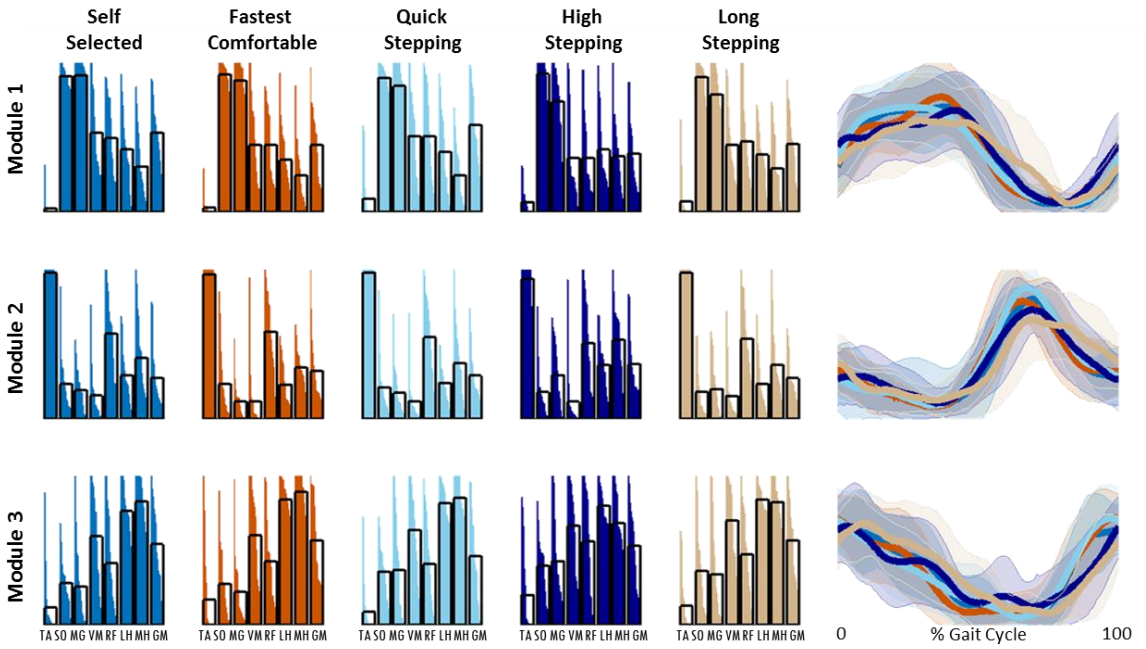

Figure 3.7: Average post-stroke subject modules for subjects with three modules are shown for all tasks. Module compositions are on the left and timing of the correspondingly colored module are on the right.

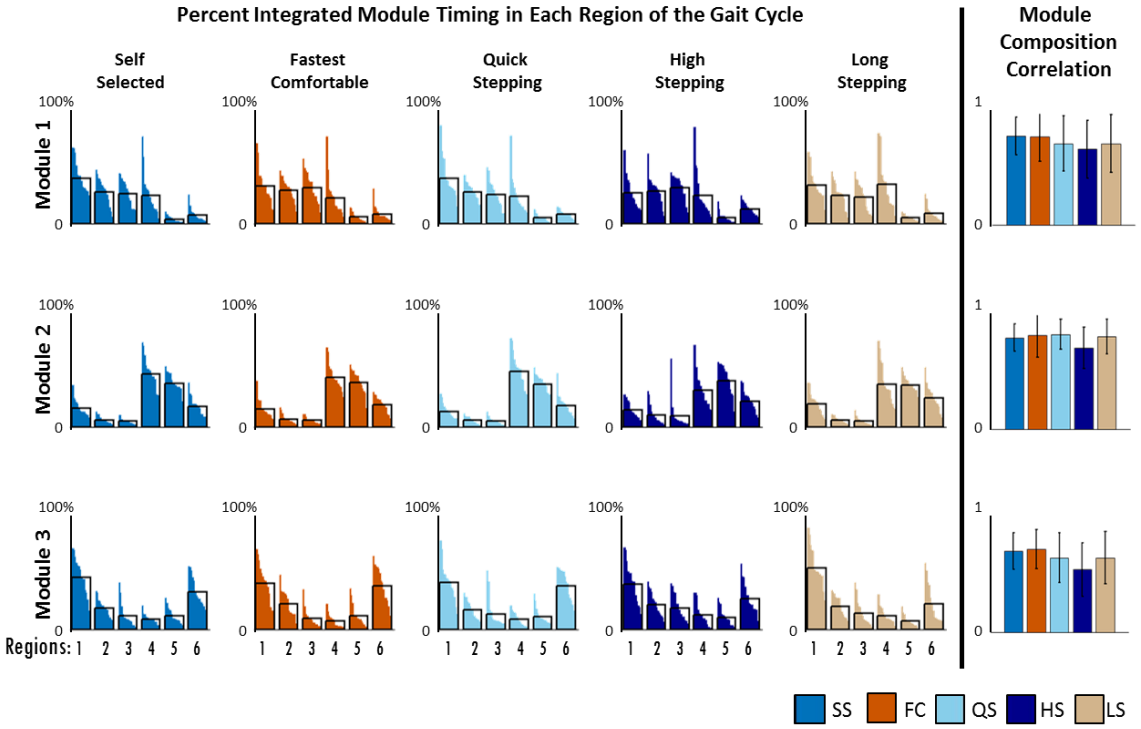

Figure 3.8: The first five bar graphs on the left represent the percent of total integrated module timing curve in each region of the gait cycle (Figure 3.1) for post-stroke subjects with three modules (n=15). ANOVAs were run for each module and region of the gait cycle across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) and "†" shows marginal significance ($\alpha<0.1$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only. The last column shows Pearson's correlations of module composition of post-stroke subjects with 3 modules to average module composition of post-stroke subjects with 3 modules. ANOVAs were run for each module across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only.

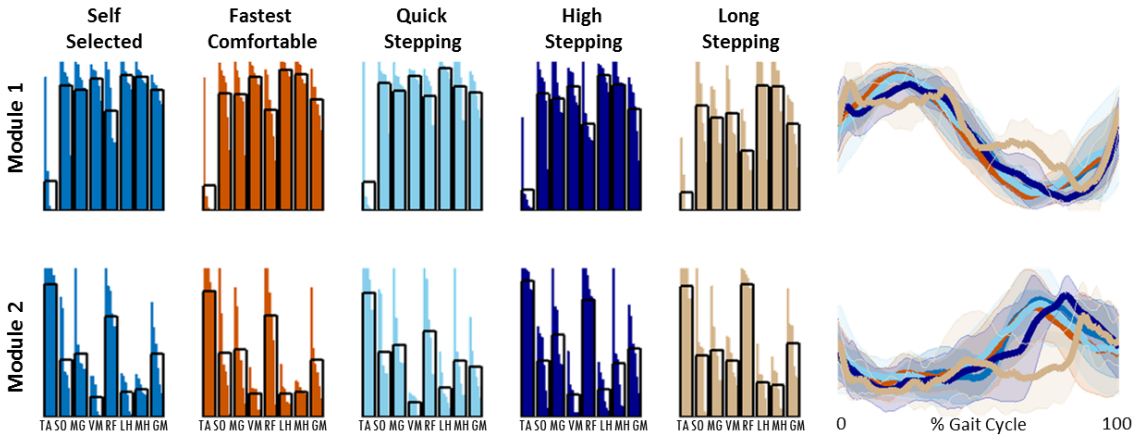

Figure 3.9: Average post-stroke subject modules for subjects with two modules are shown for all tasks. Module compositions are on the left and timing of the correspondingly colored module are on the right.

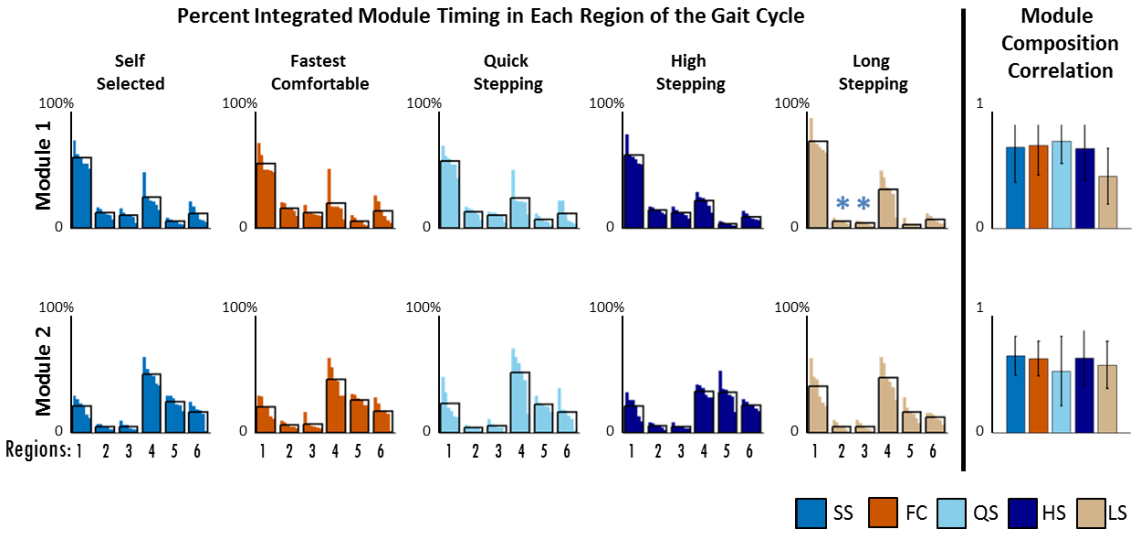

Figure 3.10: The first five bar graphs on the left represent the percent of total integrated module timing curve in each region of the gait cycle (Figure 3.1) for post-stroke subjects with two modules (n=6). ANOVAs were run for each module and region of the gait cycle across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) and "†" shows marginal significance ($\alpha<0.1$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only. The last column shows Pearson's correlations of module composition of post-stroke subjects with 2 modules to average module composition of post-stroke subjects with 2 modules. ANOVAs were run for each module across mobility capability tasks. Asterisks show significance ($\alpha<0.05$) in post-hoc t-tests with Bonferroni corrections compared to SS condition only.

Mobility capability

In addition to having lower correlations to the average control modules and more limited ability to change module timing, the post-stroke subjects were not able to perform the mobility capability measures as well as the control subjects. The ability to change speed ($p<0.0001$), cadence ($p<0.0001$), step height ($p<0.0001$) and step length ($p<0.0001$) all corresponded with the number of modules in post stroke subjects and these abilities are reduced compared to the control subjects (Figure 3.11).

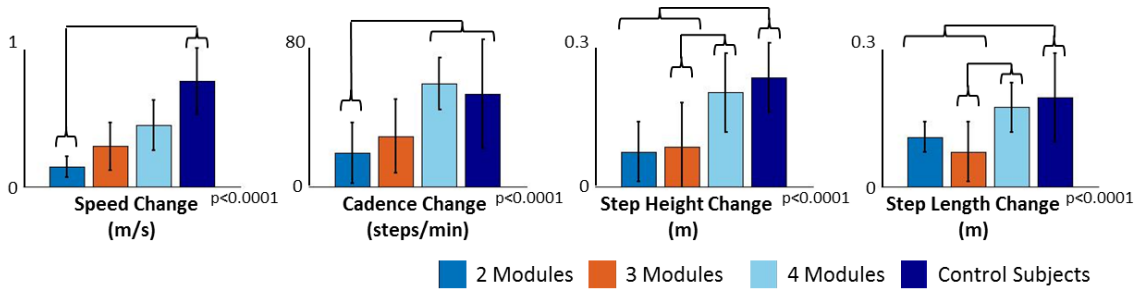

Figure 3.11: Mobility capability in each task by subject group. P-values are indicated for one-way ANOVAs across groups of subjects (e.g., Post-stroke subjects with 2 modules, 3 modules, 4 modules and Control subjects) for each mobility capability measure. Brackets indicate significance in post-hoc t-tests with Bonferroni corrections.

DISCUSSION

The goal of this study was to determine whether the same modules would be used to perform a range of locomotor tasks, with each subject modifying the timing and magnitude of those modules to adapt to the new biomechanical demands of each task. Overall, we found that for each subject the same underlying modules (number and composition) that contribute to steady state walking also contribute to mobility capability tasks (e.g., FC, HS, LS and QS) in healthy and post-stroke subjects. A difference in a module's composition would have represented an altered contribution of one or more muscle to the composition of the module during a particular task as compared to SS walking. Further, we found that subjects with fewer modules performed the tasks more poorly. Thus, our theoretical framework was mostly supported. We expected that the same modules would be used to perform the range of locomotor tasks, with each subject modifying the timing and magnitude of those modules to adapt to the new biomechanical demands of each task. Further, since we believe that the modules each result in the

performance of different biomechanical functions, we expected that the lack of four independent modules with similar composition, timing and magnitude would degrade performance of the locomotor tasks. Of particular interest, the lack of four independent modules showed up very strongly in the task performances of high stepping and long stepping, the tasks that showed the greatest changes in module timing in healthy subjects. It appears that three or two modules did not yield the adaptability of four modules and task performance suffered.

Control subjects

In healthy subjects, module timings, but not compositions, changed when the functional task demands were altered. The compositions of the four modules for all mobility capability tasks in the control subjects were consistent with control modules previously identified during steady-state treadmill walking (Clark et al. 2010; Chapter 2) and the SS walking data collected in the current study (Figure 3.3). The only significant difference in module compositions occurred in Module 4 during the LS and QS mobility tasks. This was likely due to a higher contribution of the vastus medialis in some of the subjects to Module 4 during the LS mobility task (Figure 3.3). However, the average contribution of the vastus medialis to Module 4 remained below the 0.4 threshold for being a major contributor to that module (Allen et al. 2012; Neptune et al. 2009) and neither LS nor QS module composition correlations were significantly different from the SS walking condition. In addition, all of the correlations to the SS walking composition averages were large (greater than 0.65), indicating very little variation in module compositions between each mobility task and SS walking. It is possible that average correlations as low as 0.65 may not necessarily be interpreted as similarity. However, correlations for muscle weightings for dissimilar modules have been shown to be

between 0.07 and 0.4 (Clark et al. 2010) and the range for good agreement in module similarity has been reported to start as low as 0.65 (Oliveira et al. 2013). These results are consistent with previous studies showing that module compositions remain unchanged across speeds in both running and walking (Cappellini et al. 2006; Clark et al. 2010). These findings suggest that module compositions are preserved across functional demands while walking and provide further evidence that a consistent set of neural building blocks may exist to perform a variety of human locomotor tasks.

Module timings, however, were affected by different functional demands, particularly in QS, HS and LS walking. In QS walking, all four modules had increased activation compared to SS walking in the regions preceding peak activation. In HS compared to SS walking, Module 4 had increased activation in pre-swing and early swing. Additionally in HS, Module 3 was active throughout the duration of swing versus the short burst in mid-swing during SS walking. In LS walking, Module 4 was activated later in swing and longer into stance than in SS walking. Adaptability in module timings is consistent with previous studies that show the same modules found in steady-state walking are also present in running and cutting maneuvers, but there exist differences in module timings (Cappellini et al. 2006; Oliveira et al. 2013).

Post-Stroke subjects with four modules

In addition to having reduced correlations with the average control module compositions, indicating poorer module quality (Chapter 2), the post-stroke subjects with four modules also demonstrated less adaptability in module timing with changing functional demands. In control subjects during HS there was increased Module 4 activity that occurred in pre-swing and early swing. However, in post-stroke subjects, the Module 4 activity in pre-swing and early swing was not always present. Thus, there was a higher

standard deviation in the average module timing and no significance in the comparison of percent integrated module timing for those regions compared to SS walking. This finding is consistent with previous studies showing that even though subjects may have four modules post-stroke, those modules can result in poorer walking performance and can differ in composition and timing from those in healthy subjects (Clark et al. 2010; Chapter 2).

Post-stroke subjects with less than four modules

Subjects with less than four modules post-stroke also had consistent module compositions across mobility tasks. Subjects with 3 modules post-stroke had no adaptability in module timing with the mobility tasks. In contrast, subjects with 2 modules demonstrated differences in the timing of their Module 1 (all muscles except TA and RF and consistent with merged Modules 1, 2 and 4 of the control subjects) in LS walking compared to SS walking. This decrease is not a key finding as the mid-stance region already has very little activity for that module in SS walking. Note that there was a sharp drop in performance from four to three modules in QS, HS and LS, the tasks that control subjects showed the greatest changes in module timing. Not having the four independent modules appears to greatly affect performance. Previous studies have shown that in subjects with less than four modules, the merging of modules interferes with the successful execution of specific biomechanical functions (Allen et al. 2013; Clark et al. 2010). The current study suggests that the merging of modules may also adversely affect the ability to adapt timings in order to execute task specific goals.

Mobility capability

The number of modules post-stroke not only affects walking performance (Allen et al. 2013; Clark et al. 2010; Chapter 2), but also mobility capability (Figure 3.11).

Subjects with two modules post-stroke demonstrated significantly less change in speed, cadence, step height and step length than control subjects and significantly less cadence change than post-stroke subjects with four modules. Subjects with three modules had significantly less change in step height and step length than control subjects and post-stroke subjects with four modules. This suggests that in subjects post-stroke, the number of modules is indicative of not only typical walking performance, but also of mobility capability performance. Since the number of modules can be increased with locomotor therapy, which improves gait performance (Chapter 2), it is also likely that mobility capability can also be influenced by rehabilitative therapy.

For the tasks investigated in this study, adaptability of the timing of Module 4 (hamstrings) appears particularly important; however was not modified in post-stroke subjects. Hamstring weakness and temporal irregularity are common in hemiparetic gait (Den Otter et al. 2007; Chapter 2). In healthy steady state walking Module 4 contributes to forward propulsion and accelerates the body laterally during the first half of stance and decelerates the ipsilateral leg in late swing (Allen et al. 2012; Neptune et al. 2009). Therefore, it is likely that Module 4 weakness and poor timing adversely affect mobility. Indeed, a recent simulation analysis showed that when timing of Module 4 is altered, body support, forward propulsion and leg swing are all adversely affected (Allen et al. 2013). Our study's findings further suggest that the ability to adapt the timing of Module 4 during HS and LS tasks influences the mobility capability performance.

Methodological considerations

The existence and function of muscle modules is still currently disputed (Tresch et al. 2009). We and others interpret muscle modules as fixed co-excited groups of muscles that contribute towards specific biomechanical function (Clark et al. 2010; Ting

et al. 2005). However, this interpretation is not universal. Some believe that modules may develop due to optimal control (de Rugy et al. 2013) or emerge as the result of biomechanical constraints (Kutch et al. 2012). Recent studies have provided evidence against the existence of muscle modules in finger control (Kutch et al. 2008; Valero-Cuevas et al. 2009). Yet, the lack of modules found in the finger does not definitively prove that modules do not exist in all limbs and for all mobility tasks. For example, modules have still been used to explain movements of the arm (Krishnamoorthy et al. 2007) and hand (Ajiboye et al. 2009; Gentner et al. 2006). Therefore it is possible that non-specialized and repetitive movements may still be governed by modules. Further, several simulation studies have shown the ability of a limited number of modules to produce realistic and well-coordinated locomotion (e.g., Allen et al. 2012; Neptune et al. 2009). This provides promising evidence that successful walking may be the product of ongoing modulation of the excitation modules based on task objectives and feedback of the system state. Modules have also been observed in neonates (Dominici et al. 2011) in addition to a wide range of locomotor activities in adults such as walking (Clark et al. 2010; Ivanenko et al. 2004), running (Cappellini et al. 2006), cutting maneuvers (Oliveira et al. 2013), cycling (Hug et al. 2010), and postural responses (Torres-Oviedo et al. 2007). It is possible that task and biomechanical constraints could reduce the redundancy in the system and restrict the set of muscle activation patterns observed during human locomotion. Thus our tasks may not be different enough from one another to significantly affect module number and composition. Future work should be directed at examining additional locomotor tasks and perhaps more direct measures of neural activations to provide a definitive neural basis for the existence of modules.

In addition, it is important to note that the focus of our research into modules in hemiparetic motor control in this and previous studies (Allen et al. 2013; Clark et al.

2010; Chapter 2) has been on understanding whether muscle activity exhibits independence in timing from the mass flexion and extension patterns commonly seen clinically because we wish to understand the biomechanical consequences of abnormal muscle co-activation (represented by present, absent or merged modules). Consistent with this focus, the validity of our results are not exclusively dependent on whether modules are fixed in composition or not.

Due to our limited recording of EMG from eight muscles, we were only able to identify four modules during healthy control walking. Recent studies have shown 5-6 modules are necessary to control healthy walking (Allen et al. 2012; Ivanenko et al. 2004; Neptune et al. 2009). However, the analysis revealed similar modules like those previously identified in stroke subjects with this same set of muscles (Clark et al. 2010; Chapter 2). In addition, recent simulation work has shown that the number and choice of muscles may impact number and composition of muscle modules identified (Steele et al. 2013). However, because it is not possible to collect reliable surface EMG from the majority of the lower limb muscles of stroke patients, we focused on the main contributors to biomechanical subtasks of walking. We believe that the number of muscles we collected EMG from is sufficient for the scope of this study because of way that we and others have interpreted modular analysis such that fixed groups of muscles are co-excited to perform specific biomechanical functions (Clark et al. 2010; Ting et al. 2005; Tresch et al. 1999). In addition, a recent study analyzing modules in multidirectional human locomotion (forward, backward and sideways walking) collected EMG from 25 muscles and found that 5-7 (an average of 5.8 ± 0.7) modules were sufficient to reconstruct EMG for each task with their individual-muscle evaluation criteria. Further, 4-6 modules were sufficient using a grouped-muscle criteria and consistent with previous studies (Zelik et al. 2014). This suggests that more muscles are

not essential to performing a modular analysis, as long as EMG is collected from the main contributors to the locomotor activity. Finally, our previous simulation work was able to confirm that the 4 experimentally identified modules, in addition to 2 biomodal modules, were able to produce well-coordinated walking simulations of both healthy and post-stroke subjects (Allen et al. 2013; Allen et al. 2012; Neptune et al. 2009). Thus, we are confident that the muscles from which we collected EMG were the most appropriate for our analyses. Future work will include musculoskeletal modeling and simulation studies of this data to develop a more complete understanding of the modules needed to perform specific mobility capability tasks.

In addition to modular pattern dissimilarity which reflects altered neural control, muscle weakness may also play a role in the successful execution of the mobility capability tasks. Our methods did not include an analysis to determine whether a particular subject's muscle strength was sufficient to perform the mobility capability tasks. However, the current study does provide evidence that module number and composition are associated with successful mobility task performance.

Additionally, by using the number of modules found for SS walking in each subject for all of their mobility capability tasks, we may have overlooked the ability of some subjects to change the number of modules they use for a particular task. However, a one-way ANOVA was run for *all* subjects across mobility tasks and there were no significant differences in the number of modules for any particular task.

CONCLUSION

In conclusion, we found that although some post-stroke subjects had a smaller number of modules than healthy subjects, the same underlying modules (number and

composition) in each subject (both healthy and post-stroke) that contribute to steady-state walking also contribute to specific mobility capability tasks (i.e., FC, HS, LS, and QS) in those subjects. In healthy subjects, we found that module timing, but not composition, changes when functional task demands are altered during walking. However, this adaptability in module timing is limited in post-stroke subjects, which limits their mobility capability performance. In addition, the greater number of modules post-stroke indicates superior mobility capability. Thus, we found specific tasks required greater changes in module timing and were then performed more poorly by subjects who did not have all of the independent modules. These specific tasks may provide a basis for a clinical assessment that reveals information about the status of the underlying health of neural (modular) organization. Thus, therapies targeting improved module timing adaptability during these tasks in addition to the separation of merged modules may lead to enhanced mobility capability in persons post-stroke.

Chapter 4: Modular control of walking across changing task demands in healthy gait: A simulation study

INTRODUCTION

Previous studies have shown that in healthy adults, steady-state walking may be controlled by a reduced set of co-exited muscles, or modules (Clark et al. 2010; Ivanenko et al. 2004). In addition to steady state walking, daily lower limb mobility is comprised of many diverse motor tasks including accelerating, stopping, turning and avoiding obstacles. Studies investigating healthy individuals executing tasks such as kicking a ball while walking (Ivanenko et al. 2005), running (Cappellini et al. 2006), walking with induced slipping (Oliveira et al. 2012), and running with cutting maneuvers (Oliveira et al. 2013), have identified module patterns similar to those in walking. Some of these studies also revealed adaptability in module timing (Cappellini et al. 2006; Oliveira et al. 2013) or changes in the number of modules (Ivanenko et al. 2005) in response to changing task demands. A recent study hypothesized that the central nervous system adapts the existing module structure to task demands rather than introducing new modules (Oliveira et al. 2012). Consistent with this hypothesis, we showed in Chapter 3 that the same underlying modules (number and composition) in each subject (both healthy and post-stroke) that contribute to steady-state walking also contribute to specific mobility tasks (e.g., high stepping (HS) and quick stepping (QS). In addition, we demonstrated that in healthy subjects module timing (i.e., the activation of each module over the gait cycle), but not composition (i.e., the relative weighting of each muscle in each module), changes when functional task demands are altered during walking.

Recent 2D and 3D simulation studies have shown that the biomechanical subtasks of steady-state walking (e.g., body support, forward propulsion, leg swing and

mediolateral balance control) are performed by specific modules (Allen et al. 2012; Neptune et al. 2009). Because each module contributes to specific biomechanical functions in healthy walking (Allen et al. 2012; Neptune et al. 2009), we expected that mobility tasks that require changes in specific biomechanical functions would affect the corresponding module patterns and timings associated with that function. Therefore, a lack of independent modules or a diminished ability to change the timing of a specific module, which is commonly seen in subjects post-stroke, could affect a subject's ability to adapt to changing task demands (e.g., increase step height or cadence).

The goal of this study was to use a 3D musculoskeletal model and forward dynamics simulations of healthy walking while performing specific mobility tasks (i.e., HS and QS) to further our understanding of modular control in human walking. Specifically, we analyzed the potential for each module to contribute to specific biomechanical functions including body support, forward propulsion and braking, mediolateral balance control, and leg swing control during the QS and HS tasks as compared to SS walking. The forward dynamics simulations provide a framework to quantify the differences in specific module contributions to GRF and mechanical energy necessary to satisfy the task requirement changes during specific mobility tasks and will ultimately further the understanding of overall mobility in healthy subjects (i.e., what subjects can do versus how subjects typically perform). Achieving this will help further the understanding of how the inability to modify gait in mobility tasks relates to motor control deficits, and thus enable clinical interventions guided by patient and task specific mobility goals. We expected that the same number of modules required to produce healthy steady state walking would be able to produce the mobility tasks. However, it was expected that the modules in QS and HS would have differences in module timing compared to healthy self-selected (SS) walking. Because we showed in Chapter 3 that the

primary modifications to the modules occur to the timing peaks of the ankle dorsiflexors (Module 3), and the hamstrings (Module 4) in swing and pre-swing, we hypothesized that modules that include muscles crossing the hip joint (Modules 1 and 4) in addition to ankle dorsiflexors (Module 3) would be primarily responsible for the modifications necessary to perform the QS and HS tasks.

METHODS

Experimental data

The experimental data analyzed were from the healthy control subjects presented in Chapter 3. Kinematic, kinetic and electromyography (EMG) data were collected from 17 healthy control subjects free from neurological disease and lower limb orthopedic impairments. All participants provided written informed consent and an Institutional Review Board approved the protocol.

Each subject walked on a split-belt instrumented treadmill (Bertec, Columbus, Ohio) at their self-selected (SS) walking speed in addition to a randomized block design of mobility tasks including walking at self-selected speed with maximum cadence (QS), and maximum step height (HS).

Reflective kinematic markers were placed on the limbs and torso using a modified Helen Hayes marker set. Marker locations were recorded at 120 Hz using a twelve-camera motion capture system (PhaseSpace, Inc., San Leandro, CA) and GRF data were sampled at 2000 Hz. Kinematic and GRF data were filtered using a fourth-order Savitzky-Golay (Savitzky et al. 1964) least-square polynomial smoothing filter and were resampled at 100 Hz. Kinematic and GRF data were averaged across subjects for the simulation tracking (see *Dynamic optimization* below).

EMG was collected (Motion Labs Systems, Inc., Baton Rouge, LA) bilaterally from the tibialis anterior (TA), soleus (SO), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), lateral hamstrings (LH) and gluteus medius (GM) at 1000 Hz. The EMG data were high-pass filtered with a zero-lag fourth-order Butterworth filter (40Hz), demeaned, rectified and then low-pass filtered with a zero-lag fourth-order Butterworth filter (4 Hz). The EMG data for each muscle were normalized to peak values during each trial. In addition, EMG data were time normalized to 100 percent of the gait cycle. The number of modules required to account for greater than 90 percent of the EMG variability accounted for (VAF) in each muscle was found using non-negative matrix factorization as previously described in detail (Clark et al. 2010).

Musculoskeletal model

A previously described 3D musculoskeletal model (Allen et al. 2012) was used to generate module controlled forward dynamics simulations of each mobility task. The model was developed using SIMM (MusculoGraphics, Inc., Santa Rosa, CA) and included rigid segments representing the trunk, pelvis and two legs (thigh, shank, talus, calcaneus and toes). The model had 23 degrees-of-freedom including six degrees-of-freedom at the pelvis (3 translations and 3 rotations), 3 rotations at both the trunk and hip joints, and one rotation each at the knee, ankle, subtalar and metatarsophalangeal joints. The foot-ground contact was modeled using 31 visco-elastic elements with coulomb friction across each foot (Neptune et al. 2000). The equations of motion were generated using SD/FAST (PTC, Needham, MA).

In a particular module, if the average muscle weighting across subjects was greater than 40%, that particular muscle was associated with that module. Muscles

without recorded EMGs but with similar anatomical arrangement and/or biomechanical function were included in the modules. Muscles within each module received the same excitation pattern and timing, but the magnitude was allowed to vary between muscles. Additionally, for smaller muscles not associated with a specific module, excitations were described by bimodal excitation patterns (Table 4.1). Muscle contraction dynamics were governed by Hill-type muscle properties (Zajac 1989) and muscle activation dynamics were modeled using a non-linear first-order differential equation (Raasch et al. 1997) with muscle-specific activation and deactivation time constants (Winters et al. 1988).

Table 4.1: The model was actuated with 38 individual Hill-type musculotendon actuators in each leg which are combined into 34 muscle groups and 4 modules.

Muscle Name	Muscle Group	Module
Anterior Gluteus Maximus	GMAX1	1
Middle Gluteus Maximus	GMAX2	1
Posterior Gluteus Maximus	GMAX3	1
Anterior Gluteus Medius	GMED1	1
Middle Gluteus Medius	GMED2	1
Posterior Gluteus Medius	GMED3	1
Anterior Gluteus Minimus	GMIN1	1
Middle Gluteus Minimus	GMIN2	1
Posterior Gluteus Minimus	GMIN3	1
Vastus Lateralis	LVAS	1
Vastus Intermedius	LVAS	1
Vastus Medialis	MVAS	1
Rectus Femoris	RF	1,3
Flexor Digitorum Longus	FDL	2
Lateral Gastrocnemius	LGAS	2
Medial Gastrocnemius	MGAS	2
Soleus	SOL	2
Tibialis Posterior	TP	2
Extensor Digitorum Longus	EDL	3
Tibialis Anterior	TA	3
Biceps Femoris Long Head	BFLH	4
Biceps Femoris Short Head	BFSH	4
Gracilis	GRAC	4
Semitendinosus	SM	4
Semimembranosus	ST	4
Adductor Brevis	AB	Bimodal
Adductor Longus	AL	Bimodal
Iliacus	IL	Bimodal
Psoas	IL	Bimodal
Pectineus	PECT	Bimodal
Sartorius	SAR	Bimodal
Superior Adductor Magnus	AM	Bimodal
Middle Adductor Magnus	AM	Bimodal
Inferior Adductor Magnus	AM	Bimodal
Gemellus	GEM	Bimodal
Piriformus	PIRI	Bimodal
Quadratus Femoris	QF	Bimodal
Tensor Fascia Lata	TFL	Bimodal

Dynamic optimization

Forward dynamics simulations were generated to emulate the experimentally measured kinematics, GRF and module timings in the QS and HS tasks (Figure 4.1). Simulations were generated for 120% of the gait cycle (starting 20% of the gait cycle prior to right heel-strike to allow the initial transients to decay). The simulations were subsequently analyzed from right heel-strike to right heel-strike. In each simulation (QS and HS), the muscle excitation patterns and initial joint angular velocities were optimized using a simulated annealing algorithm by minimizing the difference between the simulated and experimental kinematic, GRF and module timing data (Goffe et al. 1994). The 3D pelvis translations and rotations, 3D trunk rotations, hip, knee and ankle joint angles, 3D ground reaction forces and module activation timings were included in the cost function (Figure 4.1). To improve the tracking convergence, tracking torques using proportional control were applied at each joint to drive them towards the desired experimental kinematics (Appendix D). These tracking torques were also included in the cost function in order to minimize them (Figure 4.1).

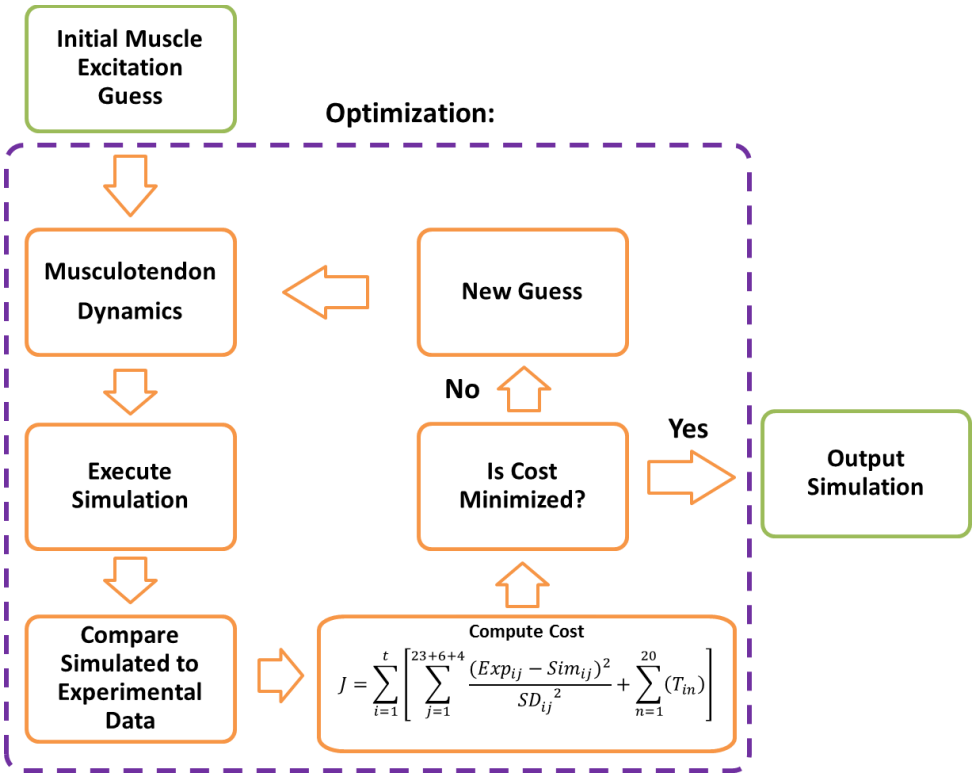

Figure 4.1: Optimization flowchart used to determine muscle excitations patterns that minimize the difference between simulated and experimental kinematics and ground reaction forces. The cost function computed differences between simulated and experimentally measured quantities (23 degrees-of-freedom, 3 GRF per leg, and 4 module patterns). Tracking torques were also included in the cost function to minimize their contributions while reproducing the experimental kinematics, kinetics and module patterns.

Simulation analyses

The HS and QS simulations were compared to a previously published control simulation (Allen et al. 2013). To assess how each module contributes to specific biomechanical functions during the QS and HS mobility tasks, the potential of each module to contribute to the biomechanical subtasks of body support (vertical GRF),

forward propulsion and braking (A/P GRF), and mediolateral balance control (M/L GRF) during stance, and leg swing control (mechanical energy delivered to and absorbed from the ipsilateral leg during pre-swing, early swing and late swing) was quantified. We used a previously described GRF decomposition and segmental power analyses (Allen et al. 2013; Fregly et al. 1996; Neptune et al. 2008; Neptune et al. 2004). A/P, vertical and M/L GRF impulses were calculated by integrating GRF contributions over the stance phase of the gait cycle. For A/P GRF, positive (propulsive) and negative (braking) GRF impulses were calculated by integrating the positive and negative contributions to the GRF, respectively. Segmental power calculations are based on the time derivative of mechanical energy and were used in this study to discuss energy flow. Total segmental power (P_j) was computed for each segment *j* as follows:

$$P_j = \left[\left(m_j \bar{a}_j\right) \cdot \bar{v}_j + \left(I_j \bar{\alpha}_j\right) \cdot \bar{\omega}_j - \left(m_j g\right) \cdot \bar{v}_j\right]$$

where m_j is the segment mass, $\bar{a}_j$ is the induced linear acceleration vector, $\bar{v}_j$ is the segment linear velocity vector, I_j is the segment inertia matrix, $\bar{\alpha}_j$ is the muscle induced angular acceleration vector, $\bar{\omega}_j$ is the segment angular velocity vector and g is the gravitational acceleration vector. Average segmental power contributions from each module to the ipsilateral leg (summed thigh, shank and foot) were calculated by averaging the segment power over pre-swing, early swing and late swing regions of the gait cycle. Positive power indicates the module acted to accelerate the leg in the direction of its motion and negative power indicates the module acted to decelerate the leg.

To perform these analyses, first the total GRF and segmental powers were calculated at each time step *i*. Then, at time step *i-1*, each muscle force was iteratively perturbed 1N and the resulting GRFs and segmental powers at time step *i* were

recomputed. Each muscle's per unit force contributions to the GRFs and segmental powers were approximated by the difference between the unperturbed and perturbed values when that particular muscle was perturbed. Each muscle's contribution to the subtasks was quantified separately and then the contribution of each module was calculated by summing the contributions of the muscles associated with that module.

RESULTS

Using the experimentally identified modules as input, the QS and HS simulations emulated the experimental data well with nearly all of the simulated kinematic data within two standard deviations of the group-averaged experimental data. The average kinematic and GRF root mean square deviations were 4.89 deg (2SD = 10.75 deg) and 0.17 BW (2SD = 0.06 BW) for QS and 7.14 deg (2SD = 11.72 deg) and 0.16 BW (2SD = 0.06 BW) for HS. Additionally, module timing curves closely matched the experimental module timings (Figures 4.2-4.3).

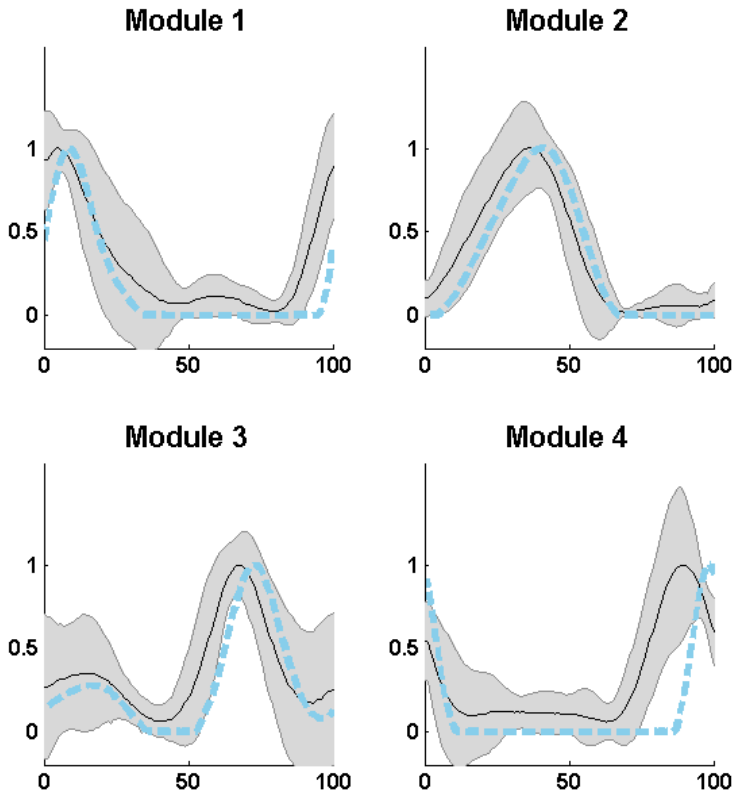

Figure 4.2: Comparison of experimental and simulated QS module timings. Average experimental QS module timings are shown ± two standard deviations (shaded in grey). The simulated QS module timings are shown in light blue.

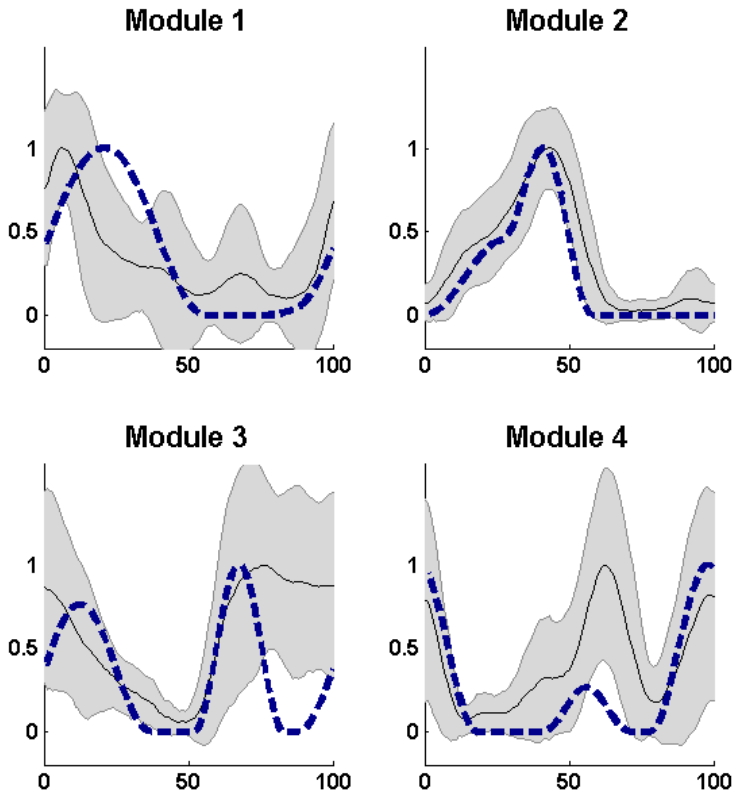

Figure 4.3: Comparison of experimental and simulated HS module timings. Average experimental HS module timings are shown ± two standard deviations (shaded in grey). The simulated HS module timings are shown in dark blue.

GRF contributions

The potential for each module to contribute to the A/P GRF was similar for all mobility tasks (Figure 4.4), however there were some minor differences. Module 1 (hip and knee extensors), generated greater braking in SS than in QS and HS. Additionally, Module 1 generated greater propulsion in HS than in SS and QS, and greater propulsion in QS than in SS. Modules 2, 3 and 4 had similar contributions to braking and propulsion across the tasks.

The potential for each module to contribute to the vertical GRF was similar for all mobility tasks (Figure 4.4) with some minor differences. Module 1 had generated greater body support in HS compared to QS and SS. Additionally in HS, Module 2 (plantarflexors) generated less body support than in QS and SS. Modules 3 and 4 had similar contributions to body support across the tasks.

The potential for each module to contribute to the M/L GRF was similar for all of the mobility tasks (Figure 4.4) with some minor differences. In HS, Module 1 generated a greater medial GRF and Module 4 generated a greater lateral GRF than in QS and SS. All modules in QS and SS had similar contributions to the M/L GRF.

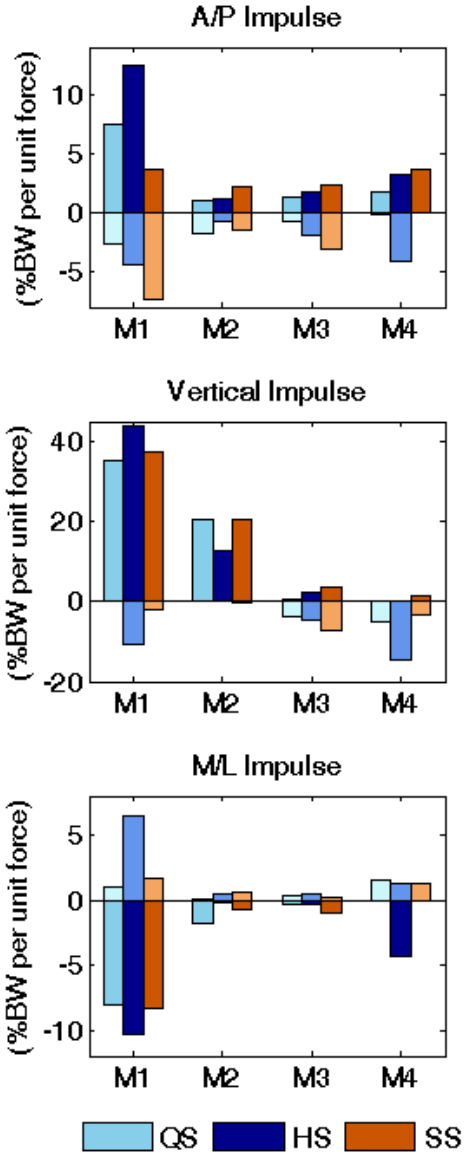

Figure 4.4: The potential for each module to contribute to the GRF impulses. QS is shown in light blue, HS is shown in dark blue, SS is shown in orange. Abbreviations: M1 is Module 1, M2 is Module 2, M3 is Module 3 and M4 is Module 4. Positive A/P values represent propulsion, negative A/P values represent braking. Positive M/L values are lateral, negative M/L values are medial.

Leg swing control

In QS during pre-swing, Module 2 delivered more energy to the ipsilateral leg than in SS and HS (Figure 4.5). In early swing, Module 3 delivered more energy to the ipsilateral leg during QS compared to SS. In late swing, Module 4 had decreased energy absorption from the ipsilateral leg during QS compared to SS.

In HS, during pre-swing, early swing and late swing, Module 4 delivered energy to the ipsilateral leg. There was no Module 4 contribution to ipsilateral leg swing in pre-swing and early swing in SS and QS. In late swing Module 4 absorbed energy from the ipsilateral leg in SS and QS. In early swing, Module 3 delivered more energy to the ipsilateral leg during HS compared to SS.

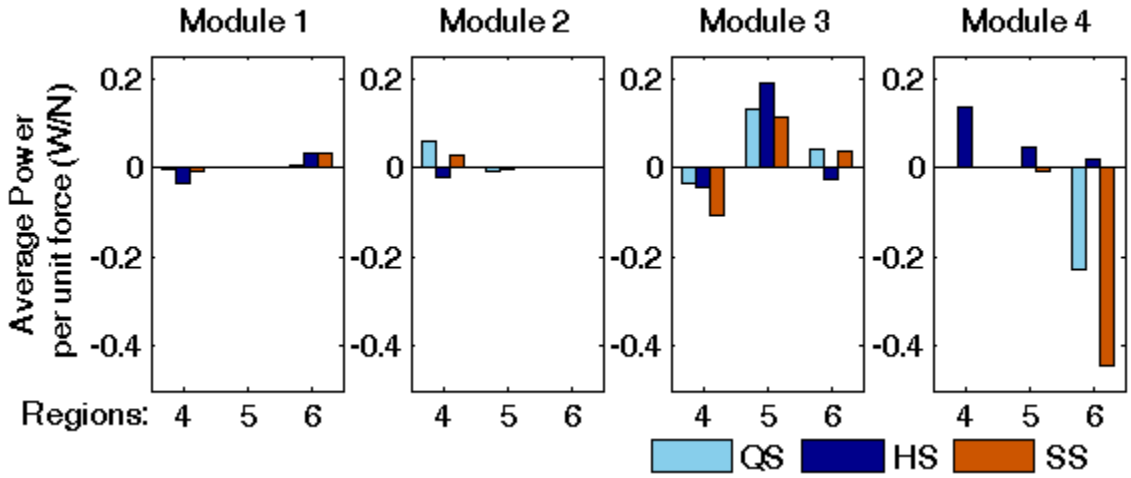

Figure 4.5: The average power (per unit force) delivered to the ipsilateral leg during pre-swing, early swing, and late swing. QS is shown in light blue, HS is shown in dark blue, SS is shown in orange. Region 4 is pre-swing, Region 5 is early swing, and Region 6 is late swing (Figure 3.1). Positive power indicates the module acted to accelerate the leg in the direction of its motion and negative power indicates the module acted to decelerate the leg.

DISCUSSION

The goal of this study was to develop forward dynamics simulations of neurologically healthy walking during specific mobility tasks (i.e., HS and QS) in order to expand the understanding of modular control of walking. As hypothesized, the same number of modules required to produce healthy steady state walking were able to produce the different mobility tasks. Module timings in QS and HS had similar modifications during the gait cycle compared to SS walking as those seen experimentally (see Figures 4.2-3; Figures 3.3-3.4).

Because the primary modifications to the experimentally measured modules in QS and HS occurred to the timing peaks of Modules 3 and 4 in swing and pre-swing (Chapter 3), it was hypothesized that modules that include muscles crossing the hip joint (Modules 1 and 4) in addition to the ankle dorsiflexors (Module 3) would primarily be responsible for the modifications to leg swing control that are necessary to perform the QS and HS tasks. Although there were some small differences in the GRF contributions, the simulated GRF for HS contained a small artifact at the beginning of stance and additional post-hoc calculations of the GRF impulses with the artifact removed revealed that all of the modules generated similar contributions to body support, forward propulsion, and mediolateral balance control during the stance phase in all the walking tasks. The primary modifications during QS and HS compared to SS occurred in the contributions from Modules 3 and 4 to swing control in pre-swing, early swing and late swing. There were minimal changes in the contributions from Module 1 to swing control during QS and HS compared to SS.

Quick stepping

Increased cadence in QS required more power from those modules contributing to leg swing in the ipsilateral leg (Modules 2, 3, and 4). In QS, Module 2 delivered more

energy to the ipsilateral leg in pre-swing than in SS. The gastrocnemius has been previously shown to accelerate the leg to initiate swing (Neptune et al. 2004). A previous study using 3D forward dynamics simulations showed an increase in the power delivered to the ipsilateral leg from the gastrocnemius when walking speed was increased (Neptune et al. 2008). Cadence increases are often associated with walking speed increases (Nilsson et al. 1987), therefore it is consistent with the previous study that QS would show similar modifications to contributions from the plantarflexors to ipsilateral leg power. In addition, Module 3, which acts to accelerate the leg into swing (Neptune et al. 2009), delivered more energy to the ipsilateral leg during early swing in QS than in SS. Finally, in QS Module 4 absorbed less energy than in SS from the ipsilateral leg during late swing resulting in less deceleration of the leg in preparation for heel-strike, which allowed the ipsilateral leg to retain more energy during the swing to stance transition.

Reduced cadence is commonly observed post-stroke (von Schroeder et al. 1995). Chapter 3 showed that even though post-stroke subjects did not have a significantly different ability to increase cadence compared to healthy subjects, post-stroke subjects with fewer than four modules were limited in their ability to increase cadence. This finding suggests that when modules are merged, subjects are unable to make necessary changes to module timing and thus are unable to provide enough energy to the ipsilateral leg in pre-swing and swing to increase cadence. Indeed, a recent simulation analysis showed that the merging of Modules 1 and 2 inhibits effective leg swing initiation in SS (Allen et al. 2013). Because Module 2 contributed more energy to the leg in order to increase cadence in healthy subjects, post-stroke subjects with merged Modules 1 and 2 would also likely have impaired ability to increase the energy provided to the ipsilateral leg in pre-swing in order to increase cadence.

High stepping

In HS, Module 4 delivered energy to the ipsilateral leg during pre-swing, early swing and late swing. This contrasted with leg swing contributions from Module 4 in SS and QS, where it did not have an effect during pre-swing and early swing and in late swing absorbed energy from the ipsilateral leg. In pre-swing and early swing in HS, Module 4 delivered energy to the ipsilateral leg. This is consistent with a previous simulation analysis that showed that when the biceps femoris is active early in swing it acts co-functionally with the illiacus to accelerate the leg (Neptune et al. 2004). In SS walking, Module 4 absorbed energy from the ipsilateral leg to decelerate the leg in late swing in preparation for heel strike (Neptune et al. 2009). In HS, Module 4 did not absorb energy from the ipsilateral leg and thus did not decelerate it prior to heel-strike. An additional post-hoc analysis of the linear components (i.e., A/P, vertical and M/L) of Module 4's contribution to the leg power revealed that during late swing Module 4 absorbed more energy in the vertical direction from the ipsilateral leg in HS than in SS walking (Figure 4.6). Indeed, with a higher step there is more motion in the vertical direction than in SS walking. Thus, increased energy absorption in the vertical direction acts to decelerate the leg as it descends from HS in preparation for heel-strike.

Similar to QS, in HS post-stroke subjects had limited ability to modify their module timings in order to take higher steps (Chapter 3). In addition, subjects with a lower number of modules had a more limited ability to take high steps. Merging of Modules 1 and 4, commonly seen post-stroke, would limit a subject's ability to independently activate Module 4 which contributed the additional energy needed to accelerate the leg into a higher step. Indeed, merging of Modules 1 and 4 has been shown to affect leg swing control in SS walking (Allen et al. 2013).

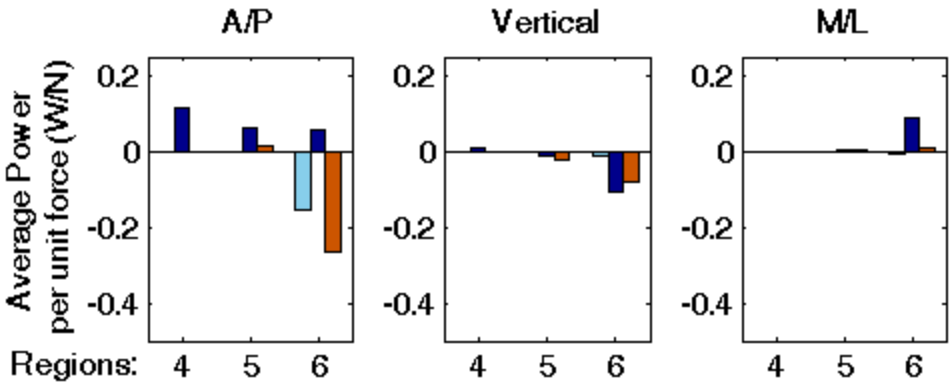

Figure 4.6: The average power (per unit force) in the A/P, the vertical and the M/L directions delivered to the ipsilateral leg during pre-swing and swing. QS is shown in light blue, HS is shown in dark blue, SS is shown in orange. Region 4 is pre-swing, Region 5 is early swing, and Region 6 is late swing (Figure 3.1). Positive power indicates the module acted to accelerate the segment in the direction of its motion and negative power indicates the module acted to decelerate the segment.

Methodological considerations

A potential limitation of this study is that the tracking torques were not completely eliminated. As a result, a per unit force perturbation analysis was used. This analysis shows the potential for each module to contribute to the biomechanical functions which is insensitive to the tracking torque contribution.

Another potential limitation of this study is that only the four experimentally derived modules were used to generate the simulations, instead of the 5-6 used in previous simulation studies (Allen et al. 2012; Neptune et al. 2009). The hip adductors, which were not included in the modules, have been shown to be important for non-sagittal plane tasks (Allen et al. 2012). However, the mobility tasks analyzed required

gait modifications primarily within the sagittal plane. Thus, the four modules were adequate to achieve the objective of this study. Future studies investigating non-sagittal plane mobility tasks (e.g. side-stepping) should include a larger number of modules.

Additionally, in this study module timings were allowed to be bimodal instead of EMG driven. This potentially limits the analysis because the exact group averaged module patterns were not replicated as in previous studies (Allen et al. 2013; Allen et al. 2012; Neptune et al. 2009). However, to reduce the difference in the experimental and simulated module timings, the module timing was included in the cost function (Figure 4.1) which resulted in similar experimental and simulated module timings (Figures 4.2-3). Thus, differences in the functional roles of the modules would be minimal.

Finally, another potential limitation of this study is that simulated GRF in HS had a small artifact at the beginning of stance. However, impulse calculations with the artifact removed showed that there were minimal differences in GRF contributions compared to SS. In addition, the primary differences between walking tasks were in the leg swing control which was consistent with the findings in Chapter 3 and the primary focus of this study. Ongoing work is to improve the simulation tracking of the GRFs.

CONCLUSION

Because modular control was able to produce well-coordinated walking simulations of HS and QS, our results support the idea that a limited number of modules are able to produce human walking with different task demands. The primary modifications to the biomechanical subtasks of walking during HS and QS occurred to ipsilateral leg swing control in pre-swing, early swing and late swing. Modules 2, 3 and 4 were primarily responsible for the modifications to the leg energetics. In QS, Modules 2

and 3 contributed more power to the ipsilateral leg in pre-swing and swing, respectively. In HS, Module 4 provided energy to the ipsilateral leg accelerating the leg into swing during pre-swing, early swing and late swing. This study provides further insight into how specific mobility tasks are performed in neurologically healthy subjects which has important implications for understanding limitations in task performance post-stroke.

Chapter 5: Conclusions

The overall goal of this research was to characterize modular organization in specific mobility tasks in post-stroke and healthy subjects and to determine whether locomotor therapy can influence module quality and walking performance. Experimental analyses were used to compare module number, composition and timing in hemiparetic subjects before and after rehabilitative therapy (Chapter 2) and within the context of different mobility tasks (Chapter 3). Simulation analyses were then performed to understand how modules contribute to important biomechanical subtasks during specific mobility tasks (Chapter 4). The results of this research provide rationale for using rehabilitative therapy to improve modular organization and provide insight into using modules as a potential assessment tool that can be used to develop rehabilitation interventions that are task-specific and target specific deficits.

The results from Chapter 2 showed that in subjects with four modules pre- and post-therapy, locomotor training resulted in improved timing of the ankle plantarflexor module and a more extended paretic leg angle that allowed the subjects to walk faster and with more symmetrical propulsion. In addition, subjects with three modules pre-therapy increased their number of modules and improved walking performance post-therapy. Thus, locomotor training has the potential to influence module composition and timing, which can lead to improvements in walking performance. This work was published in *Gait & Posture*.

Routson, R.L., Clark, D.J., Bowden, M.G., Kautz, S.A. and Neptune, R.R. (2013). **The influence of locomotor rehabilitation on module quality and post-stroke hemiparetic walking performance**. *Gait & Posture* 38(3): 511-517.

The results from Chapter 3 showed that although some post-stroke subjects had a smaller number of modules than healthy subjects, the same underlying modules (number and composition) in each subject (both healthy and post-stroke) that contributed to steady-state walking also contributed to specific mobility tasks (i.e., high stepping, long stepping and quick stepping). In healthy subjects, module timing, but not composition, changed when the functional task demands were altered during the various mobility tasks. However, this adaptability in module timing in addition to mobility performance was limited in post-stroke. Specific tasks that required greater changes in module timing were performed more poorly by subjects who did not have all of the independent modules. This work was published in *Physiological Reports*.

Routson, R.L., Kautz, S.A. and Neptune, R.R. (2014). **Modular organization across changing task demands in healthy and post-stroke gait.** *Physiological Reports* 2(6): 1-14.

The simulation analysis in Chapter 4 showed that the chief modifications to the biomechanical subtasks of walking occurred in the control of leg swing during pre-swing and swing. In quick stepping, Module 2 (plantar flexors) and Module 3 (tibialis anterior and rectus femoris) contributed more power to the ipsilateral leg in pre-swing and swing, respectively, than in self-selected walking. In high stepping, Module 4 (hamstrings) provided energy to the ipsilateral leg that accelerated the leg into swing in pre-swing and swing. These specific tasks may provide a basis for a clinical assessment that reveals information about the status of the underlying health of neural (modular) organization. Thus, therapies targeting improved module timing adaptability during these tasks in addition to the separation of merged modules may lead to improved walking performance in persons post-stroke. This work is being prepared for submission to *Clinical Biomechanics*.

Routson, R.L., Kautz, S.A. and Neptune, R.R. (2014). **Modular control of walking across changing task demands in healthy gait.** *Clinical Biomechanics (in preparation).*

Chapter 6: Future Work

The overall goal of this work was to further the understanding of modular control in post-stroke and neurologically healthy walking and mobility-related tasks. The results provided insight into mobility performance deficits caused by merged and irregular module patterns. The results also provided rationale for using locomotor rehabilitation therapy to decouple merged modules and improve the quality of the module patterns. This work can be expanded in several different areas.

In Chapter 3 we showed that fewer modules were indicative of poorer overall mobility task performance and hemiparetic subjects were not able to significantly modify their module timings during the mobility tasks. Additionally, Chapter 4 provided insight into the contributions of modules to specific biomechanical subtasks during the mobility tasks in neurologically healthy subjects. A previous study showed that the merging of specific modules manifests itself in predictable deficits in biomechanical functions (Allen et al. 2013). Additional experimental and simulation analyses should be performed to understand how specific merged patterns affect mobility task performance, ability to modify module timings and the differences in contributions of these merged modules to biomechanical subtasks in mobility tasks. Thus, furthering the understanding of how specific module complexity, compositions and timings are limiting mobility performance. Also, only two of the many possible merged patterns were considered in the prior study (Allen et al. 2013). However, in the dataset analyzed in Chapter 2 additional merged patterns were observed in the post-stroke subjects. Further simulations are needed to investigate contributions to biomechanical tasks from other specific merged patterns.

In Chapters 3 and 4, gait was modified from self-selected level walking to show overall mobility performance. However, these modifications were relatively small and it is unclear whether the same modules activated during level over-ground walking are shared across other motor tasks such as stair climbing, walking on uneven terrain, and stepping over obstacles. For example, stair climbing is biomechanically different from walking and provides a functional measure in the lives of persons with mobility disorders (Stratford et al. 2006). Due to its importance and prevalence in daily life stair climbing ability in stroke survivors is often used as a predictor of independent living (Ghafari et al. 2009). Because stair climbing is important to daily life, it is essential to understand whether the modules that account for walking also account for stepping up in young healthy adults. A pilot study investigating a step-up task showed an additional module comprised of quadriceps activity was necessary (Appendix E). The emergence of this module when stepping up varies from the results in Chapter 3 with HS but is consistent with a prior study which observed voluntary tasks like kicking a ball or obstacle avoidance contain separate activations timed to the voluntary task (Ivanenko et al. 2005). Further experimental and simulation analyses are needed to further the understanding of healthy modules during various tasks, like the step-up task, which will ultimately allow us to understand how altered module organization in impaired populations adversely affects task performance. This information could then be used to develop rehabilitation interventions that target specific deficits in a variety of tasks, not just level walking.

The work in the dissertation focused on understanding modular organization as a clinical tool specific to post-stroke mobility. However, the existence and function of muscle modules is disputed (Tresch et al. 2009). Important future work should investigate whether there is a neural link to modular control of gross movements such as walking. In post-stroke gait, the first step is to understand if the location of lesion correlates with

specific modular organization (i.e., number of modules, and module quality). Additionally, it is important to begin investigating whether other impairments that affect specific portions of the brain and spinal cord such as multiple sclerosis and Parkinson's disease affect modular organization and whether the changes to modular organization are stereotypical for a particular impairment. This would provide further insight into how specific brain impairments affect modular organization, thus furthering the link between modular organization and altered neural control.

Appendix A: Non-Negative Matrix Factorization (NNMF)

The EMG data were high pass filtered with a cutoff frequency of 40 Hz, de-meaned, low pass filtered with a cutoff frequency of 10 Hz using a 4th order Butterworth filter and normalized to its overall peak values. Gait cycle time was determined from the GRF data. All data were time normalized to 100% of the gait cycle. For each subject, the number of modules required to account for >90% of the EMG variability was found using a non-negative matrix factorization algorithm (Figure A.1) (Clark et al. 2010; Lee et al. 1999).

The EMGs were combined into a non-negative $m\ x\ t$ matrix (EMG_O) where m is the number of muscles ($m = 8$) and t is the number of strides x 101. A priori, the number of modules (n), were specified and the non-negative matrix factorization was implemented for $n = \{1,2,3,4,5\}$. For each repetition of non-negative matrix factorization, the matrix EMG_O was approximated such that $EMG \approx WH$, where the $n\ x\ t$ matrix H is a set of n basis vectors specifying the activation timing of a module in the gait cycle and W is an $m\ x\ n$ matrix representing each muscle's contribution to the composition of the modules. When multiplied together the result is EMG, which is an approximation of the original matrix EMG_O. The matrices H and W begin with random initial guesses and are optimized until the difference between WH and EMG is minimized. This is done using a Euclidean distance cost function ($J = ||EMG - WH||^2$) and a multiplicative update algorithm (Figure A.1).

The reconstructed EMG using non-negative matrix factorization (EMG_R), was found by multiplying the final W by the final H. The ratio of the sum of the squared error to the sum of the squared original EMG (EMG_O), was used to quantify the variability accounted for (VAF) for the number of modules (Figure A.1). The number of modules

was increased until VAF exceeded 90% for all muscles and regions of the gait cycle or until adding an additional module did not increase VAF by 5% for the muscle or region with the lowest VAF.

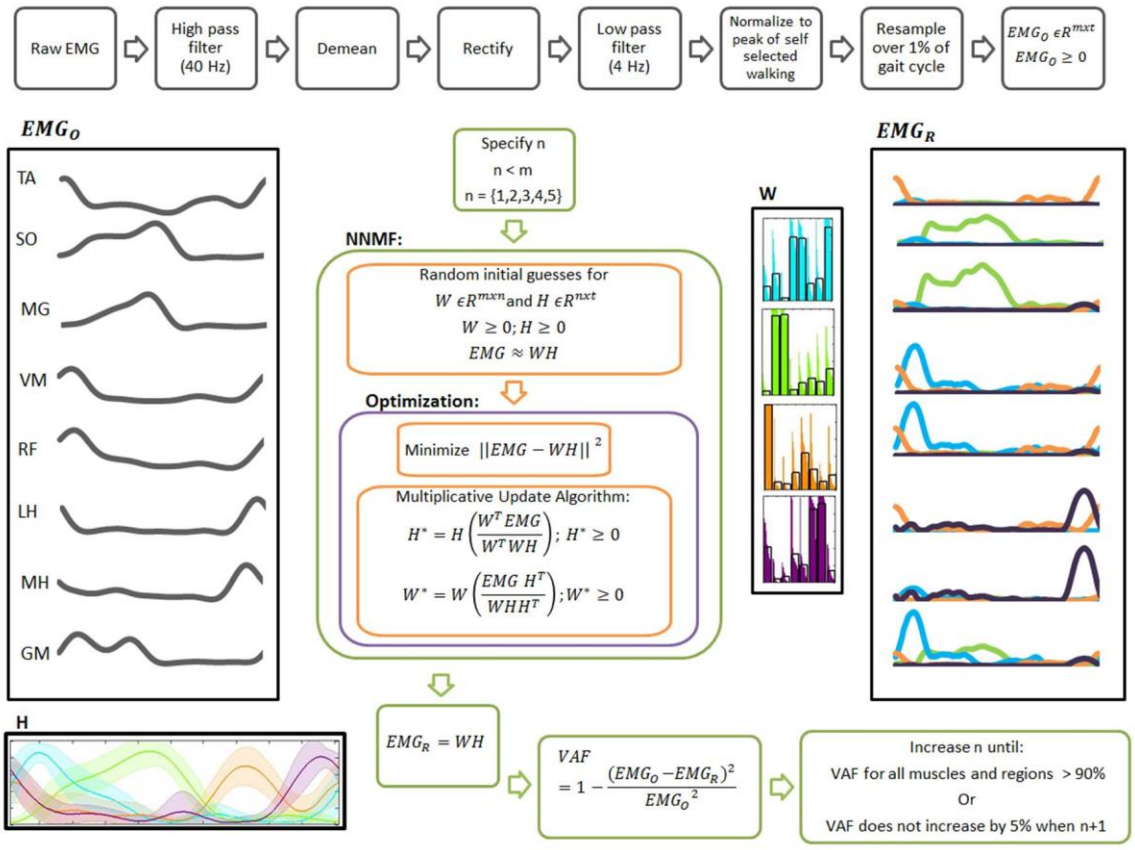

Figure A.1: EMG processing and Non-negative Matrix Factorization (NNMF) algorithm. *n* is the number of modules. NNMF is run iteratively for various values of *n*, which are specified a priori. *W* is the composition of the modules, *H* is the timing of that module in the gait cycle. EMG_O and EMG_R refer to the original and reconstructed EMG, respectively. *VAF* is the variability accounted for. The optimization uses a multiplicative update algorithm to minimize the Euclidean distance between the EMG_R and EMG_O signals.

Appendix B: Linear Discriminant Analysis (LDA)

The goal of using the Linear Discriminant Analysis (LDA) was to automate the sorting of modules. Sorting modules into similar categories is typically based on finding the major contributors to that module and assigning them to the correct module such that Module 1 consists primarily of the hip and knee extensors, Module 2 consists primarily of the ankle plantarflexors, Module 3 consists primarily of the tibialis anterior and rectus femoris, and Module 4 consists primarily of the hamstrings. Healthy modules are generally consistent with high Pearson's correlations to the average module composition. However, even when post-stroke subjects have four modules, these modules often have low similarity to those of healthy subjects and manually sorting these modules can become a cumbersome task. However, it is important that the modules are sorted such that when compared with control subjects for quality, we have an accurate picture of the altered neural control. Therefore, I used LDA as a tool to automate the module sorting process.

In multiclass LDA (Rao 1948), an observed variable (x) needs to be assigned to one of many groups or classes based on the characteristics or value of x. A training set of data is used to create linear projection vectors such that when the data of the training set is projected onto them, there is a maximum of separation between the means of the classes. The observation (x) can then be assigned to the class with the maximum posterior class probability. The LDA algorithm that was used to assign individual post-stroke modules to a particular module number using the previously sorted healthy module data as the training set to create the four classes (one for each healthy module) into which we wished to sort new observations. Then each individual hemiparetic module was sorted based on the training set. The maximum likelihood that any particular hemiparetic

module belonged to Module 1, 2, 3 or 4 was indicated as a probability. Table B.1 shows the results of the LDA for the post-stroke subject data used in Chapter 2. This table shows the posterior class probability for the modules of subjects who had four modules post-therapy. Here, each hemiparetic module was compared to the training set (healthy subject modules) and sorted based on the highest probability (likelihood) that the unsorted module should be assigned to that class (assigned module). The maximum posterior probability for a particular unsorted module to belong in one of the four classes is highlighted. Examples of resorted module data based on Table B.1 are show in Figures B.1-B.3.

Table B.1: LDA analysis for post-therapy subjects with 4 modules. The highest probability (out of the four possible healthy modules) for a particular hemiparetic module is in the column labeled "_INTO_". Highlighted cells show maximum posterior probability for a particular unsorted module to belong in one of the four classes. Red text indicates modules that may have been previously sorted incorrectly. Red Text: PL14*, PL24*, PL25*, PL31*, PL32, PL34, PL35, PL36, PL37, PL38*, PL39. The "*" indicates possible need for resorting.

			Predicted Module1					Predicted Module2					Predicted Module3					Predicted Module4				
Subject	Pre	NICP	Module1	Module2	Module3	Module4	_INTO_	Module1	Module2	Module3	Module4	_INTO_	Module1	Module2	Module3	Module4	_INTO_	Module1	Module2	Module3	Module4	_INTO_
PL01	4	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL10	4	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL12	4	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL13	4	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL14	4	4	0.993	0.000	0.007	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	0.000	1.000	Module4	0.000	1.000	0.000	0.000	Module2
PL21	4	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL24	4	4	0.000	0.000	0.000	1.000	Module4	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.999	0.000	0.001	0.000	Module1
PL25	4	4	0.000	1.000	0.000	0.000	Module2	0.000	0.967	0.000	0.033	Module2	0.000	0.000	1.000	0.000	Module3	1.000	0.000	0.000	0.000	Module1
PL29	4	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL04	3b	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL09	3b	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL11	3b	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	0.999	Module4
PL17	3b	4	0.998	0.000	0.000	0.002	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL27	3b	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	0.131	0.869	Module4	0.002	0.998	0.000	0.001	Module2
PL28	3a	4	0.392	0.608	0.000	0.000	Module2	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL30	3a	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL18	3c	4	0.982	0.000	0.000	0.018	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	0.996	0.004	Module3	0.785	0.000	0.101	0.114	Module1
PL20	3c	4	0.053	0.000	0.000	0.947	Module4	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.004	0.000	0.036	0.959	Module4
PL31	3c	4	0.000	1.000	0.000	0.000	Module2	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.000	0.000	0.000	1.000	Module4
PL35	3c	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	1.000	0.000	Module3	0.946	0.000	0.000	0.054	Module1
PL26	2	4	0.831	0.000	0.000	0.169	Module1	0.582	0.145	0.273	0.000	Module1	0.000	0.000	1.000	0.000	Module3	0.000	1.000	0.000	0.000	Module2
PL38	2	4	1.000	0.000	0.000	0.000	Module1	0.000	1.000	0.000	0.000	Module2	0.000	0.000	0.783	0.217	Module3	1.000	0.000	0.000	0.000	Module1

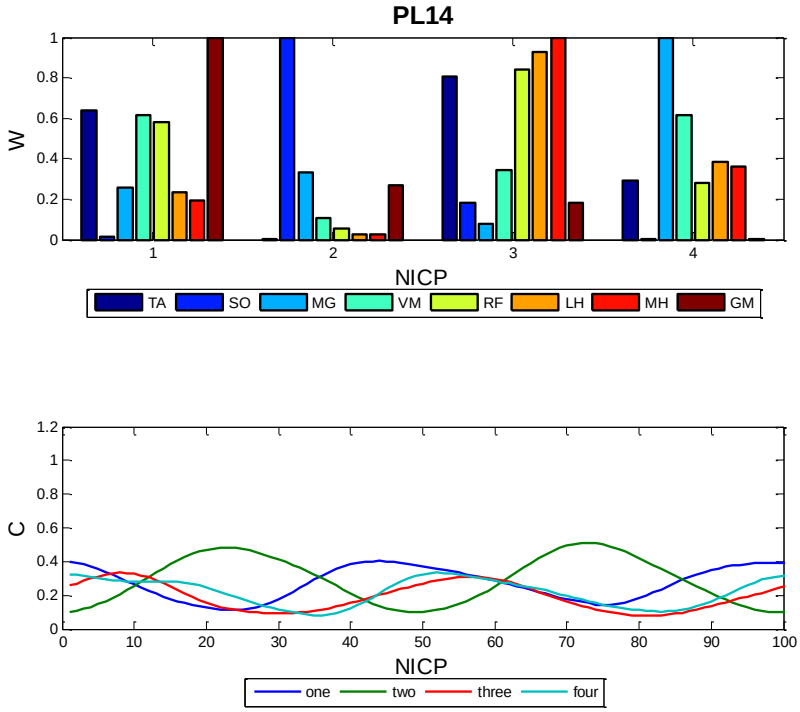

Figure B.1: This figure shows module assignments prior to LDA sorting. In subject PL14, previously assigned Module 3 was sorted as Module 4 when using LDA because of high hamstring contribution. Previously assigned Module 4 was sorted as Module 2 using LDA because of the high gastrocnemius contribution.

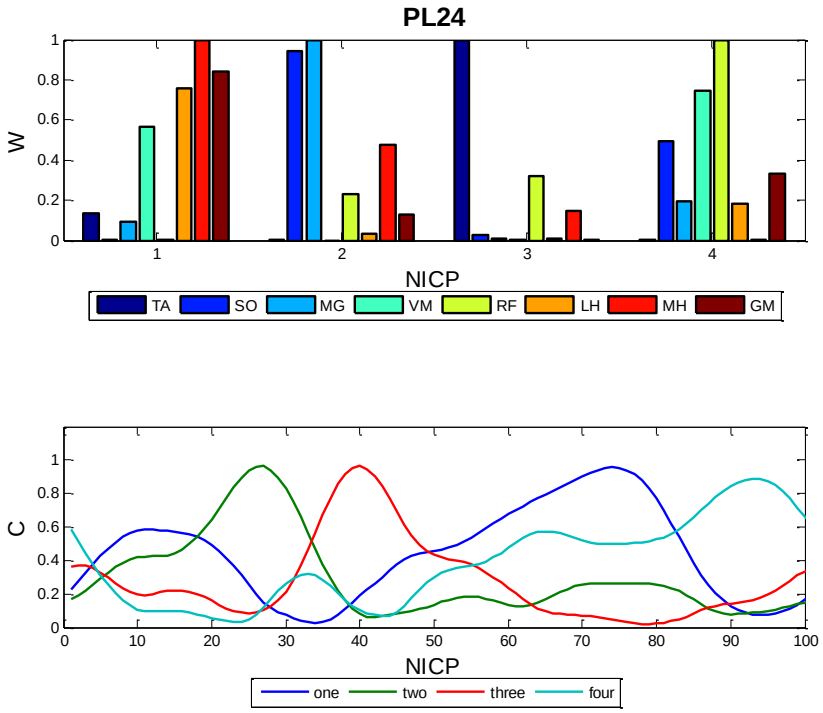

Figure B.2: This figure shows module assignments prior to LDA sorting. In subject PL24, using LDA previously assigned Module 1 was sorted as Module 4 and previously assigned Module 4 was sorted as Module 1 because of the high hamstring contribution in previously assigned Module 1.

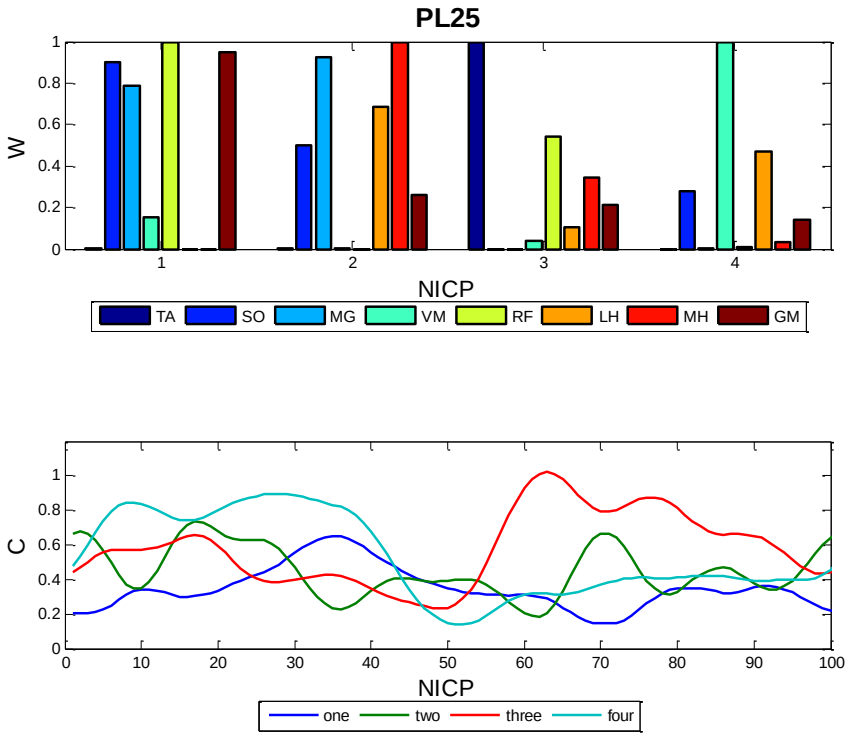

Figure B.3: This figure shows module assignments prior to LDA sorting. In subject PL25, using LDA previously assigned Module 4 was sorted as Module 1 because of high VAS contribution, previously assigned Module 1 was sorted as Module 2 because of high plantarflexor contributions and previously assigned Module 2 was sorted as Module 4 due to high hamstrings contributions.

Appendix C: Goal Programming

In optimization, treating some objectives as constraints instead of objectives allows more flexibility in the optimal solution. This is called goal programming. Goal programming was implemented into my simulated annealing algorithm in Chapter 4 to allow for more flexibility in the optimal solution and help the algorithm to converge to be within two standard deviations of the grouped average data.

In the cost function, at each time step (*t*) for each degree of freedom (*i*) if the difference between the simulated ($q_i(t)$) and experimental ($\tilde{q}_i(t)$) kinematic angles was greater than a constant (*k)* multiplied by the standard deviation ($SD_i(t)$) the cost for that degree of freedom for that time step ($C_i(t)$) was calculated. If the difference was not greater, the cost for that degree of freedom for that time step was set equal to zero. The cost was calculated such that the error only accumulated after being greater than the constant multiplied by the standard deviation (Equation C.1).

$$C_i(t) = \left(\frac{[q_i(t) - \tilde{q}_i(t)] - k * SD_i(t)}{SD_i(t)}\right)^2 \qquad \text{Equation C.1}$$

Appendix D: Tracking Torques

The tracking torque at each joint (one for each degree of freedom except the pelvis translations) was calculated using the difference between the simulated and experimental angles. To ensure a smooth transition of the torque application, a logistic function was used. The torque was only applied once the joint angle error was greater than ***k*** standard deviations of the experimental joint angle as follows:

$$T_i(t) = A * [q_i(t) - \hat{q}_i(t)] \frac{1}{1+\exp\left(\frac{B}{k*SD_i(t)}[q_i(t)-\hat{q}_i(t)]+C\right)} \qquad \text{Equation D.1}$$

where $T_i(t)$ is the applied torque at time t for joint i, $\hat{q}_i(t)$ is the experimental joint angle position at time t for joint i, $q_i(t)$ is the simulated joint angle at time t for joint i, $SD_i(t)$ is the standard deviation at time t for joint i, A is the proportional gain, and B and C are the logistic function parameters and are equal to 91.9 and 87.3, respectively. The values for B and C were chosen such that the logistic function multiplier is zero until the joint error equals 90% of two standard deviations of the experimental data and is equal to one when the error is equal to two standard deviations of the experimental data. In the knee joint, different values of k and A were assigned for different regions of the gait cycle (e.g., swing versus stance), where the change in gain and number of standard deviations allowed for better tracking. An example of tracking torque calculation is shown in Figure D.1.

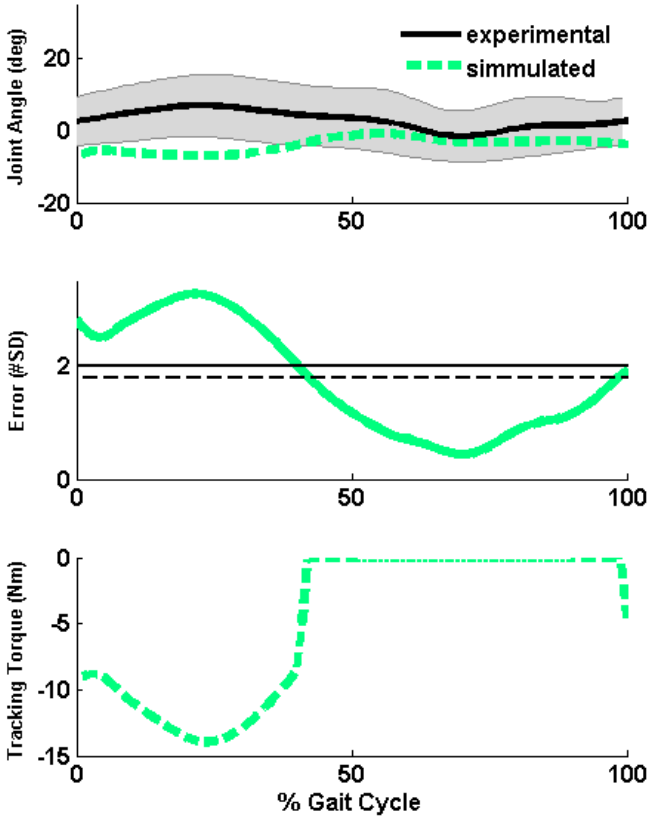

Figure D.1: Example of tracking torque calculation. Top: Experimental (green dashed line) and simulated (dashed solid line) joint angle. Gray region represents ±2 SD. Middle: Error between the experimental and simulated joint angle normalized by the SD (green solid line). The tracking torque does not turn on until the error reaches 1.8 SD (dotted black line). Bottom: The resulting tracking torque (green line).

Appendix E: Modular Organization in a Step-Up Task – A Pilot Study

INTRODUCTION

In healthy adults, experimental analyses of modular organization have shown that well-coordinated walking may be produced by exciting four co-excitation modules: Module 1 (hip and knee extensors) in early stance, Module 2 (ankle plantarflexors) in late stance, Module 3 (tibialis anterior and rectus femoris) during the stance to swing transition, and Module 4 (hamstrings) in the swing to stance transition. However, compared to healthy subjects, post-stroke hemiparetic subjects display poor inter-muscular coordination characterized by dissimilarity in module composition and timing from those of healthy subjects and often have a reduced set of modules (Clark et al. 2010). Given that modules control the biomechanical subtasks of movement (Neptune et al. 2009), a reduced set of modules suggests the biomechanical subtasks of walking may be interfering with one another, thus adversely influencing walking performance (Allen et al. 2013). Therapies that restore normal module timing and composition could improve locomotor performance.

However, it is unclear whether the same modules activated in level over-ground walking are shared across motor tasks such as stair climbing and stepping over obstacles. For example, stair climbing is biomechanically different from walking and provides a functional assessment measure for those with mobility disorders (Stratford et al. 2006). Due to its importance and prevalence in daily life, stair climbing ability in stroke survivors is often used as a predictor of independent living (Ghafari et al. 2009). Because stair climbing is important to daily life, it is essential to understand if therapies that target improving modules in level walking also target the same modules used in a step up task.

Therefore the purpose of this pilot study was to determine if the same modules associated with level over-ground walking are also associated with a step-up task in young healthy adults.

METHODS

Four subjects completed 25 over-ground walking trials and 25 step-up trials. Step up tasks were completed by taking several level steps prior to stepping up onto a platform and bringing the trailing leg up to match. Marker data were collected for the heel, toe, metatarsophalangeal and ankle joints of each subject. Heel strike was determined as the minimum position of the heel marker. Foot strike on the step was determined from the minimum toe marker velocity. The gait cycle while stepping up was assessed from heel-strike to foot-strike (onto the step) of the foot that stepped onto the step last.

EMG data were collected from 8 muscles bilaterally: tibialis anterior (TA), soleus (SO), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). EMG were high pass filtered (40Hz) with a zero lag fourth-order Butterworth filter, rectified, and smoothed with a low pass (4 Hz) zero lag fourth-order Butterworth filter. Average EMGs of the contralateral leg were investigated.

Using a non-negative matrix factorization algorithm (Clark et al. 2010), the number of modules required to account for the EMG variability were assessed. The number of modules was determined using a VAF threshold of 90% for each muscle (Clark et al. 2010). The number of modules was increased until all regions and muscles achieved VAF of >90% or if adding an additional module did not increase VAF by >5%.

RESULTS AND DISCUSSION

Most subjects (*n=3*) had four modules during over-ground walking which were phase shifted (due to being from the contralateral leg), but similar in composition and timing to previous literature (Clark et al. 2010). Similarly, most subjects (*n=3*) had four modules during the step-up task. These modules were similar to over-ground walking, except the plantarflexor module was missing in all subjects and an additional independent module consisting of the quadriceps muscles was present in all subjects. A recent study hypothesized that the central nervous system adapts the existing module structure to task demands rather than introducing new modules (Oliveira et al. 2012). In contrast, the step-up results show that new modules may be introduced when tasks are functionally different from level walking. However, the results of this pilot study are consistent with another recent study which observed in voluntary tasks like kicking a ball or obstacle avoidance separate activations timed to the voluntary task occur (Ivanenko et al. 2005).

Quadriceps muscles act synergistically to support the body and raise the body's COM during stair climbing (Ghafari et al. 2009). Indeed, movement in the extension phase is mostly due to extensor activity about the knee (McFadyen et al. 1988). This would explain the timing burst for the quadriceps module timed during the extension phase in the step-up task. However, in contrast with previous work showing EMG in stair assent (McFadyen et al. 1988), in this pilot study there was no longer a clear bust of plantarflexor activity. Because the plantarflexor module acts functionally to create forward propulsion (Neptune et al. 2009), the lack of an independent plantarflexor modules is consistent with the lack of forward propulsion needed during the step-up task.

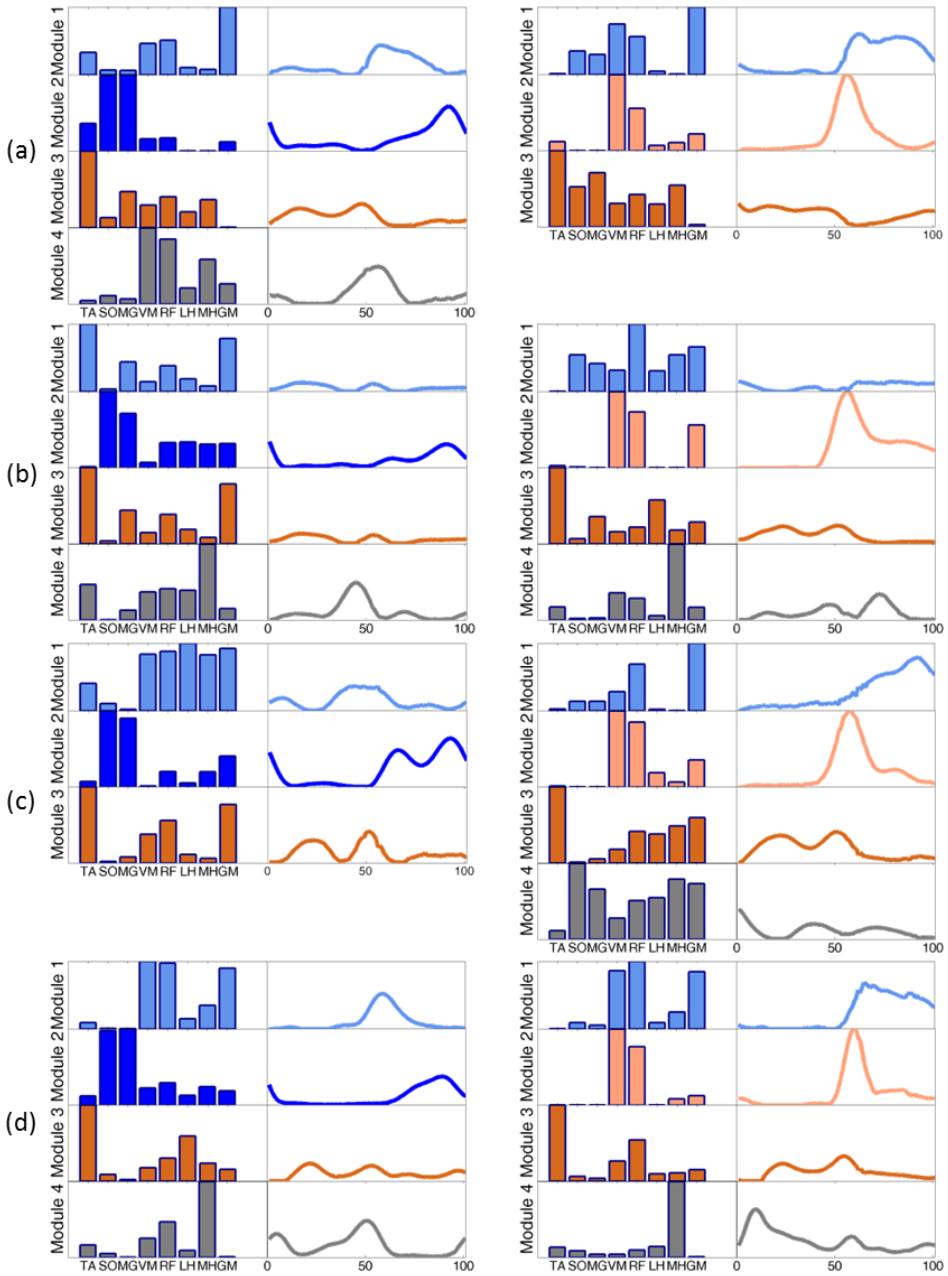

Figure E.1: Module Composition (left pane of each column) and Timing (right pane of each column) for each subject (each row) for over-ground walking (left column) and step up (right column) tasks. Abbreviations (in order from left to right): TA, tibialis anterior; SO, soleus; MG, medial gastrocnemius; VM, vastus medialis; RF, rectus femoris; LH, lateral hamstrings; MH, medial hamstrings; GM, gluteus medius. Module 1 is light blue, Module 2 is dark blue, Module 3 is dark orange, Module 4 is grey, and the Quadriceps Module is light orange.

Methodological considerations

A potential limitation of this study is that it investigated a step-up task where movement was terminated after both feet were on the platform. In tasks of daily living, it is likely that after the step-up task there would be ascension up additional steps or subsequent level walking. However, the results of this study meet the study goals which were to investigate if modular organization was modified during a step-up task. Future work should investigate differences in modular organization when subjects transitions to additional locomotor tasks of daily living.

CONCLUSION

While performing the step-up task, subjects developed a new module compared to level-walking comprised of quadriceps muscle activity. Future work should investigate a larger number of subjects so that a statistical analysis can be performed. This work will provide further information about modular organization in a step-up task which is an important mobility task and predictor of independent living in impaired populations. Therefore, this would be the first step in understanding if therapies that target improving modules in level walking also target the ability to step up.

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Vita

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