MEASUREMENT OF ACTIVITY SPECIFIC BEHAVIORAL RECOVERY IN CHRONIC STROKE

By

MARK GOODMAN BOWDEN

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By

Mark Goodman Bowden

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Current examinations of post-stroke motor control rely on interpretation of isolated movements performed during standardardized clinical examinations. Due to the complexity of human walking, however, evaluation of walking specific motor control likely needs to be conducted as the patient is ambulating. Task specific evaluations may enhance the ability of the clinician to distinguish recovery of functional behavior by means of compensation for motor control deficits from true restitution of walking specific motor control. The purpose of this dissertation is to examine assessments by which individuals post stroke may be examined during walking in order to distinguish restitution of physical function from compensatory responses. Current clinical examinations do not differentiate motor activity during the task or in walking and correlate poorly with functional and biomechanical walking performance measures. Factor analysis of electromyographic motor patterns, however, yields specific modules of activity that correlate significantly with each of the examined walking performance measures. Voluntary, discrete activities may be inadequate to capture the complex motor behavior in walking, and walking specific measures are required to describe the efficacy of rehabilitation on behavioral recovery. One such measure is derived from the anterior-posterior ground reaction forces

generated during walking. These forces are responsible for the propulsion of the center of mass anteriorly and we propose a measure (paretic propulsion) that allows for examination of the paretic leg contribution to overall propulsion. This measure is positively correlated both with speed and with severity of hemiparesis. Perhaps most importantly, paretic propulsion allows the investigator to distinguish functional compensation from physiological restitution by providing a measure of coordinated output of the paretic leg. Additionally, we assessed measures of spinal level reflex activity to examine the degree to which those with post stroke hemiparesis modulate sensory input. While healthy controls modulate in a systematic and reproducible fashion, those with stroke demonstrate substantially more variable responses. We determined that paretic leg responses differ depending on side stimulated, indicating that stroke leads to altered function at the level of the spinal cord during gait. Further exploration is required to fully understand the motor control and clinical implications.

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CHAPTER 1
LITERATURE REVIEW

Introduction

The present moment may be the most optimal time in history to be involved in rehabilitation research. Technology is progressing rapidly, improving our ability to provide interventions and capture necessary, quantifiable data to measure capacity and performance. Translational research is bridging the gap between basic and clinical sciences, and partnerships spanning research domains are allowing scientists to grow knowledge at an unprecedented rate. Neuroscientists and clinicians have not always used the same language to communicate findings and suggestions, however, and it is imperative that the rehabilitation community institute a common framework to guide communication for all individuals participating in the broad spectrum of activities from scientific inquiry to patient care. A potential mechanism by which such a framework may be achieved is by providing definitions within the structure and understanding of the rehabilitation models that are currently accepted as critical in international rehabilitation research. As Alan Jette stated in a recent review of rehabilitation models, a framework demonstrates great potential "to provide the rehabilitation disciplines with a universal language with which to discuss disability and related phenomena" (Jette, 2006). Application of current growth is dependent upon a structural framework that allows researchers and clinicians to understand and communicate common interests and findings in a way such that science may be moved forward optimally.

One area in which the nomenclature creates confusion is the discussion of recovery versus compensation as it relates to neuroanatomy, physical impairments after neurologic injury, and functional performance. For example, the term "recovery" has been used somewhat interchangeably to refer to the amelioration of structural deficits within the nervous system and

the improvement seen at a functional level as the result of a neurorehabilitation intervention (Levin et al., 2008). This functional "recovery", however, does not often distinguish between a return to a pre-pathological pattern of functioning and an adaptive compensatory response relying on altered performance of varying effectors within the system. Examining functional improvements to distinguish restitution of physical performance from compensatory adaptations requires a level of measurement that is currently sparse and largely unapplied to the field of rehabilitation in general, and neurorehabilitation specifically. Current tools for assessing the functionality of walking are based on physical performance measures such as walking speed, distance walked, physical independence, use of adaptive equipment and/or orthotic devices, and observational methods of balance control. However, improvements in all of the above may be attained via compensation of other limbs and body segments, and in fact tell the observer very little of the degree of functional restitution.

The purpose of this dissertation is to provide assessments by which individuals post stroke may be examined during the functional activity of walking in order to distinguish restitution of physical function from compensatory responses. This literature review aims to introduce: 1) the significance of the problem of impaired walking post stroke; 2) the need for quantification of physical performance measures; 3) the International Classification of Functioning, Disability, and Health (ICF) and how this model can help define recovery versus compensation; 4) the literature relative to examination of biomechanical factors of hemiparetic walking that assist in explaining walking specific motor control post-stroke; 5) a standardized measure of motor control post-stroke, the Fugl-Meyer Assessment (FMA) and how quantification of RMA results may elucidate walking specific motor control post-stroke; and 6) a proposal for a method of

exploring if impairments in modulation of spinal level cutaneous reflexes relate to impaired biomechanical and functional walking performance in a sample of individuals post-stroke.

Significance of Problem

Stroke is one of the most debilitating medical conditions in America, affecting approximately 750,000 people each year with a surviving cohort of nearly 8 million people (Gresham et al., 1995). Hemiparesis, strictly defined as a muscular weakness or partial paralysis of half of the body, is seen in three-quarters of persons post-stroke. Seventy-three percent of those surviving stroke will have some degree of long term disability (Gresham et al., 1995), and less than 50% of survivors progress to independent community ambulation (Perry et al., 1995a). Even among those who achieve independent ambulation, significant residual deficits persist in balance and gait speed, with 60% of persons post-stroke reporting limitations in mobility related to walking (Gresham et al., 1995) Given that in persons post-stroke, improving walking speed is 1) independently related to overall health status (Studenski et al., 2002); 2) a strong predictor of functional recovery (Richards et al., 1995c); 3) reflective of both physiological and functional changes (Bowden et al., In Press); and 4) the most often stated goal during rehabilitation following a stroke (Bohannon et al., 1988), interventions aimed at improving walking speed, and by implication functional walking status, are an important goal. This goal for effective therapy creates a critical need to measure the effect of the intervention as well as predict appropriate candidates for therapy. As many contemporary therapeutic approaches are based on activity based therapies targeting available plasticity of the central nervous system, it becomes even more paramount to develop and utilize measures that accurately capture the results of task specific interventions.

Need for Quantification of Rehabilitation Research Findings

Accurate and reliable measures are vital in order to interpret findings accurately, regardless of the domain of rehabilitation models in which one focuses his or her research. Without appropriate measures, all research findings are subject to threats of internal validity (the degree to which changes in the dependent variable are caused by careful and controlled manipulation of the independent variable) and external validity (the degree to which you can make inferences from a study to the general population). Measurement lies in the ability to represent the targeted construct accurately, and too often existing outcomes represent different or multiple constructs. True objective measurement may be defined as "repetition of a unit amount which maintains its size with an allowable range of error no matter which instrument is used to measure the variable of interest (test free) and no matter who or what relevant person or thing is being measured (sample free)" (personal communication, Craig Velozo). In the above definition, all measurement is an approximation of a perfect concept, which itself is an abstraction. An example would be the concept of length, which is a perfect abstraction as it has neither a maximum nor a minimum value. The ruler, a common tool to measure length, is not perfect as there will always be a degree of error associated with its use. However, the ruler is an appropriate representation of the construct of length. The ruler is standardized, sample free, test free, efficient, and precise, thus meeting the criteria defined above.

Much of the historical "measurement" in rehabilitation resides at the level of rankings and scores based on observation. Research focused on body structures and functioning, however, requires precise instrumentation and quantification techniques. Biomechanical measurements of joint angles, ground reaction forces, velocity, and acceleration are appropriate quantifications of the proposed constructs associated with human movement and force production. Similarly, EMG signal amplitude, frequency, and timing are appropriate for measuring the construct of

neural activation to a muscle. However, unclear definitions of constructs and the use of ordinal level measurement continue to exist, even within the level of body function research.

In the past decade, researchers have begun using quantifiable biomechanical measures as outcome measures for interventions based on amelioration of impairments such as decreased strength (Gregory et al., 2007; Parvataneni et al., 2007; Teixeira-Salmela et al., 1999) and for task-specific interventions such as locomotor training (McCain et al., 2008; Sullivan et al., 2006). However, these assessments are technologically and monetarily costly and require a great deal of time to complete, making their application in the clinic almost impossible. In fact, a 2001 survey of European rehabilitation centers, only six out of 68 centers (~9%) were using any type of technological assessment tool routinely, and these were primarily limited to video analysis and goniometry (van Wijck et al., 2001). Interestingly, five of these six centers were associated with educational institutions, and only 2/3 of the responding centers even had access to any type of technological assessment tool. Barriers to implementation included a lack of money, lack of training, insufficient technical support, and a lack of information.

Perhaps even more troubling is the fact that only approximately half of the centers used at least one non-quantifiable assessment scale in at least 75% of the cases (van Wijck et al., 2001). The most common pattern seen in neurorehabilitation clinics was a “basket” of assessment tools including the Modified Ashworth Scale (for spasticity assessment), the Functional Independence Measure (to assess independence in activities), and the Fugl-Meyer Assessment (to assess stroke-specific motor control) (van Wijck et al., 2001). Barriers to implementation of measurement included a shortage of time, a lack of information, a lack of training, or the fact that the tests were too “cumbersome”. This particular survey did not address how tools were used, nor did it address the issue of standardization, but previous reports have documented a lack of

standardization between rehabilitation facilities (Wade, 1992). Of great importance is how these instruments may provide valid information regarding severity of the construct or how such information may guide interventions.

Clearly, more work needs to be completed within the rehabilitation research community not only to develop quantifiable tools to capture meaningful information about individual's impairments and performance, but also to develop clinical analogues that delineate similar information. Furthermore, necessary education, training, and support need to be provided to clinicians in conjunction with the academic community to assist the use of quantifiable information in the treatment planning and program implementation for those with neurological injury.

International Classification of Functioning, Disability, and Health (ICF)

In 2001, the World Health Organization (WHO) attempted to clarify the original rehabilitation model put forth by Saad Nagi (Nagi, 1965) in order to achieve the following: 1) redefine the components of the model; 2) make the model multidirectional; 3) clearly define the environmental and personal factors that contribute to the model; and 4) combine medical and social models of disability. In addition, the ICF model was designed as a classification system to be used in concert with the WHO's International Classification of Diseases, Tenth Revision (ICD-10). Combined, these systems systematically group health and health related domains in an attempt to develop a "meaningful picture of the health of people or populations" in order to be used for "decision-making purposes" (WHO, 2001).

The new definitions of the ICF are as follows (Figure 1-1) (WHO, 2001):

- BODY FUNCTIONS. "physiological or psychological functions of body systems "(WHO, 2001).
- BODY STRUCTURES: "anatomic parts of the body such as organs, limbs, and their components" (WHO, 2001).

- ACTIVITY: "execution of a task or involvement in a life situation in a uniform environment (capacity)" (WHO, 2001).

- PARTICIPATION: "execution of a task or involvement in a life situation in an individual's current environment (performance)" (WHO, 2001).

- ENVIRONMENTAL FACTORS: "the physical, social and attitudinal environment in which people live and conduct their lives" (WHO, 2001). Environmental factors may either be individual (including home, workplace, and school as well as the direct contact one may have with others in this environment) or societal (other social structures, services, and systems that may have an impact on an individual).

- PERSONAL FACTORS: "the background of an individual's life and living, and are defined by the features of the individual that are not part of a health condition or health state"(WHO, 2001). Examples of personal factors include gender, race age, lifestyle habits, upbringing, coping styles, social background, education, experiences, character style, and psychological assets.

One of the clear changes in the ICF model compared to previous models of disablement is the inclusion of environmental and personal factors as contributors to the overall health condition of an individual. While other models imply an environmental impact and contribution, the ICF defines and clearly delineates the contributions of the environmental and personal factors. In contrast to the Nagi model and the first generation WHO model, where there is a progression as the environment becomes disabling, the ICF recognizes that environmental and personal factors are pervasive throughout the model and can affect body structures and functioning as well as activity and participation. Because of the interconnectedness of the model, intervention at a particular area has the potential of impacting any other area of the model.

In further contrast to the Nagi model, the ICF is not limited to discussion of the pathological condition, but rather is designed to describe the health status of any individual. In a healthy population, the model describes normal body structure and function, activities, and participation whereas they describe impairments, activity limitations, and participation restrictions in those in an abnormal health condition (WHO, 2001). Furthermore, one does not have to demonstrate a progression linearly through the model. As examples: 1) someone with a

physical disfigurement (impairment) may not have activity or participation limitations; 2) societal stigma associated with a diagnosis may limit participation in the absence of impairments; and 3) the use of adaptive equipment may reduce or decrease activity limitations and participation restrictions even in the presence of profound impairment. Lastly, in contrast to earlier models, the ICF allows for the presence of indirect impairments, which are not caused by a disease process directly, but instead are sequelae to disease and processes. As an example, an acute spinal cord injury does not lead directly to decubitus ulcer formation, but instead ulcers form secondary to factors such as prolonged immobility, reduced nourishment, and maceration.

The ICF makes unique contributions in its ability to 1) define health status for both impaired and non-impaired individuals; 2) allow for entrance into the model at any point and not rely on progression from one extreme to the other; and 3) account for indirect effects of pathological states. For these reasons, the ICF has been adopted as the model of choice locally by the College of Public Health and Health Professions and was recently adopted nationally by the American Physical Therapy Association as its model of choice to guide rehabilitation efforts. For my particular area of research interest, the above advantages of the ICF are particularly salient in defining and quantifying the subtasks of human locomotion.

Within the context of the above definitions of body structures and activity, the concepts of recovery and compensation may take on different meanings. At a neuronal level, most researchers would agree that the term recovery in stroke connotates “reactivation in brain areas previously nonactivated by the circulatory event” (Levin et al., 2008). When discussing functional recovery, however, researchers and clinicians alike fail to distinguish if recovery occurs at a body structure or activity level. Current assessment tools focus on task accomplishment as opposed to discriminating the mechanistic underpinnings of how the task is

performed. As Levin recently stated, “we have to demonstrate that functional motor outcomes are superior when therapeutic intervention is aimed at the reacquisition of motor elements underlying functional task accomplishment” (Levin et al., 2008). If patients are identified who fail to recover at a functional level, we may determine either that the intervention was insufficient to promote recovery or that some patients may lack the capacity for task-specific motor learning. This failure to distinguish adequately the effect of the interventions not only limits determination of therapeutic efficacy, but it also fails to distinguish those who may maximally benefit from recovery-based interventions from those who would perhaps optimize functional performance with a compensatory approach. The ability to customize interventions to maximize the motor learning potential of the individual is dependent upon accurate understanding and measurement of structural impairments as well as functional performance.

Building on the ICF’s definition of body structure/functioning, Levin posits that recovery at this level is characterized by “restoring the ability to perform a movement is the same manner as it was performed before injury” relying on pre-morbid levels of strength, range of motion and movement patterns (Levin et al., 2008). Conversely, compensation at the body structure/function level requires performing a movement in a new manner and is characterized by altering degrees of freedom through co-contraction, altered timing, and altered combination of movements (abnormal synergies). Similarly, recovery of activity level performance revolves around successful task accomplishment using pre-morbid effectors, while compensation allows for functional success with altered effector usage when compared to pre-morbid or healthy control patterns. Clinical examinations such as manual muscle testing and spasticity assessment may give accurate information as to the recovery of body structure impairments while giving very little information regarding how this structural recovery relates to functional recovery.

Conversely, functional assessments such as walking speed provide a great deal of information about expected functionality (Perry et al., 1995b) but does not tell the examiner how that function was attained. A full battery of examination is required at both the body structure and activity levels, measuring both recovery and functional capacity in order to move therapeutic interventions forward for true customization and optimization of care.

The experiments described within this proposal focus primarily on measures of recovery at the activity level of the rehabilitation model and the relationship between recovery and performance based measures of walking performance. This framework offers the potential to further understand walking performance and thus improve upon the next generation of interventions designed to assist those with stroke relation hemiparesis improve walking function.

Biomechanical Examination of Hemiparetic Walking

As deficits in walking performance post-stroke are related to a reduced ability to produce forces necessary to advance the center of mass and limbs forward during walking, quantifiable techniques are required to assess this ability during the task. One mechanism by which this may be accomplished is through examination of the surface electromyographic (EMG).

Electromyography

EMG illustrates the electrical signal that occurs when the motoneuron communicates with the muscle to activate muscle firing. EMG analysis has been used for many years as a way to evaluate neuronal activation of the muscles. This activation can be described temporally, defining the firing of different patterns of activity in locomotor-specific patterns during the gait cycle, and amplitude, which attempts to quantify neuronal input by the amount of voltage in the electrical signal. EMG signals are alternating current, so initially signals are rectified to arrange all of the signals in the positive direction and then filtered to remove unrepresentative spikes in amplitude. EMG signals also contain a great deal of noise and variability, making interpretations

on a single or few gait cycles problematic at best (Knutson and Soderberg, 1995). For this reason, the preferable analysis involves averaging over several gait cycles, an analysis that is made easier by the multiple gait cycles that are collected in walking trials on an instrumented treadmill. To complete this analysis, however, the data must be normalized temporally, meaning that each cycle must be identified from 0% to 100% by some external indicator. In the experiments in the Human Motor Performance Laboratory, this is achieved by identifying foot contact via GRFs on the treadmill. Once temporally, normalized, separate gait cycles may be averaged together, creating an "ensemble average of linear envelops", controlling for variability and noise through the averaging of multiple trials.

Additionally, background EMG must be taken into account to glean out resting electronic signals from those associated with walking behavior. Simply taking the lowest activity in the cycle as "rest" is insufficient as postural stabilization muscles must be activated, and this activity is not "normal" particularly in the neurologically impaired population (Knutson and Soderberg, 1995). Resting EMG in our protocols is quantified during a quiet sitting activity. EMG by itself only relates one mechanism associated with walking behavior. For example, electrical activity does not distinguish between concentric and eccentric contractions, nor does it explain the kinesiological correlates that are happening concurrently.(Knutson and Soderberg, 1995) Additional factors such as energy absorption and generation, limb positioning, and joint moments must be considered as well.

A second mechanism of investigating motor control biomechanically incorporates an analysis of ground reaction forces (GRF). These investigations lead to the ability to examine movement of the center of mass as well as to calculate joint moments, powers, and work relative

to specific phase of the walking cycle. Definitions and importance of moments, work, and power will be described later in this section.

GRFs are derived from Newton's third law, stating that for every action there is an equal and opposite reaction. In the study of human motion, this law indicates that all surfaces provide a reaction force and that the individual is acted upon by that force when s/he is in contact with that surface (Hamill and Knutzen, 1995). In human motion analysis, the study of this reaction is achieved via the use of a force plate which measures the vector describing the force acting upon the individual. This vector is comprised of three orthogonal components: the vertical force; the anterior/posterior force; and the medial and lateral force. Analysis of these individual components within the context of a free body diagram allows investigators to summarize all of the forces acting on a system at any particular time and describe the joint reaction force at a particular joint. Extrapolation of these forces in a distal to proximal direction allows for the calculation of subsequent joint reaction forces and is the basis for the inverse dynamics approach to human motion analysis (Hamill and Knutzen, 1995). These calculations allow for determination of the previously mentioned moments, power, and work.

Moments

During walking, moments describe the summary torque that results around any joint during the gait cycle and is required to maintain dynamic stability of the system by preventing collapse when gravity leads to instability. These moments are calculated as the product between the GRF vector and the limb segment vector when analyzed together in a kinetic chain. For example, a plantarflexor moment occurs during the gait cycle as the tibia passes over the foot stationary on the ground. The muscle activity at this time produces plantarflexion for stability, even though the movement at the time is in a dorsiflexion direction.

Power

Power is computed by calculating the product between moments and angular velocity. When moments and angular velocity are both positive, then the power is positive indicating a net production of energy. When the moments and velocity have a different sign, as when the moment is positive and the angular velocity is negative, the power is negative indicating a net absorption of energy, although this absorption may not be at the same rate as the previously described energy expenditure (Beltman et al., 2004). Considering the example of the tibia moving over the stationary foot, the moment is plantarflexion, but the velocity is slowing, stabilizing the movement and preparing for limb advancement, indicative of an a power absorptive phase.

Work

Mechanical work describes the amount of force used to move an object a particular distance as defined by the formula W=F x s (distance). For example, in an isometric contraction in which no movement occurs, no work is done even though a considerable amount of force may be generated. In the field of motion analysis, it is often a simpler calculation, however to describe work as a product of power and time which may be calculated by determining the integral of the power curve between two defined time points (eg. the beginning and the end of a stance phase).

Over the past 20 years, investigators have begun using biomechanical analyses to investigate the contributing mechanisms to impaired walking post-stroke. In particular, power and work are often used to describe the capacity to produce the required mechanics for steady state walking. In 1991, Olney published a seminal description of work and power in the hemiparetic population (Olney et al., 1991). In this study, Olney describes both positive work (integral of positive power curves) and negative (integral of negative work curves), as both are

indicative of energy expenditure. In particular, the following phases of the gait cycle contribute to mechanical work being performed by each leg: positive work by the ankle plantarflexors during terminal stance/push-off (A2); negative work by the knee extensors during weight acceptance (K1) and at push-off (K3) and positive work during midstance (K2); negative work by the knee flexors during terminal swing (K4); positive work by the hip extensors in early stance (H1) and early swing (H3, also termed "pull-off"), and negative work through mid to late stance (H2). These values were calculated for both the paretic and non-paretic legs.

As a result of this work, Olney determined that regardless of walking speed, the paretic leg contributes approximately 40% of the positive work being performed (Olney et al., 1991). The profiles between the two legs visually appear very similar, with the primary difference being one of amplitude, and Olney concludes that the compensation assumed between the legs is minimal. These mechanical work estimates, however, rely on assumptions as to the recovery of mechanical work from individual sources and intercompensation between sources (Aleshinsky, 1986) and do not describe what functional tasks are being accomplished by the work. Forward dynamic simulation models have demonstrated that more of the mechanical work performed during a gait cycle is done in early single leg stance in order to raise the body's center of mass (COM) than occurs in double limb support (DLS) prior to swing, which primarily provides forward propulsion and swing initiation (Neptune et al., 2003). The power produced during DLS likely decreases even more in those with slower walking speeds, implying that an even higher proportion of work is done to raise the COM.

The mechanical work estimates provided by Olney thus may not describe the task of propelling the body forward during walking, which is an essential requirement of locomotion (Shumway-Cook and Woollacott, 2001), and instead may more accurately describe the role of

the hemiparetic leg to support body weight during stance. Subsequently, additional measures are required to describe adequately the critical role of moving the body forward during locomotion and to assess if these measures are sensitive to levels of hemiparetic severity. Therefore, the purpose of the first study in this dissertation is to examine anterior/posterior GRFs as an appropriate method of measuring the contribution of the paretic leg to the coordinated task of forward propulsion during walking.

Examination of Post-stroke Motor Control

Motor recovery post-stroke is difficult to measure, and theories surrounding motor function post-stroke have been dominated by the concept of progressing through predictable stages of recovery (Brunnstrom, 1966; Twitchell, 1951). This progression is based on the organization of reflex behavior, theorizing that severe impairments reflect a return to previously assimilated primitive reflexes. According to this theory, primitive reflexes provide the necessary background for more complicated voluntary movements (Fugl-Meyer et al., 1975). Someone with non-flaccid paralysis (preservation of reflexes) presents with a recovery of motor function in a regular sequence in which initial movements are dependent on reflex-based synergistic movements. Patients recovering from stroke gradually develop fully integrated voluntary movement patterns, relying less on reflexive behavior (Brunnstrom, 1966). Based on this theory, Fugl-Meyer in 1975 developed a measurement instrument reflecting this reflex hierarchy to quantify recovery post-stroke (Fugl-Meyer et al., 1975). This instrument is divided into upper extremity and lower extremity components focusing on distinct constructs such as reflexes, movement control, coordination and speed, with an additional section specific to balance recovery (Fugl-Meyer et al., 1975). Specifically, the lower extremity motor evaluation (FM-LE) consists of a total score of 34 points with 17 items scored on a 0-2 scale. In addition, an 11-item

(22 points) sub-section of the FM-LE is dedicated to analysis of abnormal movement synergy patterns (FM-S) and excludes the reflex and coordination/speed parameters.

The FM-LE, however, is based on voluntary, discrete tasks based on the dominant influence of cortical input on motor control. In addition, the FM-LE examines motor control in three theoretically progressive positions: supine, sitting, and standing. However, the motor control deficits that the FM measures may differ from deficits seen during task specific activities such as walking. A recent study investigated the abnormal movement patterns seen post-stroke by analyzing strength deficits and movement patterns from a "functionally relevant" standing position (Neckel et al., 2006). The authors found although those with stroke were significantly weaker than neurologically healthy control subjects. Those with hemiplegia and controls used similar strategies to achieve movements. In fact, only during maximal hip abduction did a significant secondary movement of hip flexion emerge in those with hemiplegia, mimicking the abnormal synergy patterns described by Brunnstrom and Fugl-Meyer (Brunnstrom, 1966; Fugl-Meyer et al., 1975). These results suggest that the primary impairment in post-stroke motor control is weakness, and that correct interpretation of post-stroke motor control can only be gleaned from positioning that is relevant to the targeted behavior. These findings are consistent with task specific approaches to studying behavior such as walking.

Based on the original work by Graham Brown, (Brown, 1911) scientists have more recently investigated the role of the spinal cord in the control of walking. After long-term training involving manual assistance from trainers, cats with severed thoracic spinal cords were able to step on a treadmill with full weight bearing at varying speeds (Barbeau and Rossignol, 1987; Lovely et al., 1986). Spatiotemporal characteristics, kinematics, and EMG responses all approximated normal cats at comparable speeds (Barbeau and Rossignol, 1987). These studies

also indicate the importance of specificity of the intervention as those cats that were trained to walk could do so but demonstrated limited capacity for static standing, while those cats stand-trained were successful in standing but not walking (Hodgson et al., 1994). Furthermore, the training effects were reversible as stand-trained cats could successfully complete walking training, and those cats trained to walk were capable of stand-training Both groups that were retrained demonstrated reduction of the originally trained skill (Hodgson et al., 1994). These discoveries were in sharp contrast with the previous assumption of the immutability of spinal cord function and laid the foundation for interventions aimed at the possibility of the spinal cord's ability to modulate peripheral input and to learn motor tasks.

The presence of walking capacity in the absence of any supraspinal input gave rise to the description of central pattern generators (CPGs). CPGs are thought to be located at the level of the spinal cord and can be the controller of rhythmic patterned behavior such as walking (MacKay-Lyons, 2002) and breathing (Barlow and Estep, 2006). CPGs can coordinate cyclic activity in the lower extremities and may be driven supraspinally or peripherally, and peripheral sensory signaling "provide cues that enable the human lumbosacral spinal cord to modulate efferent output in a manner that may facilitate the generation of stepping" (Harkema et al., 1997). This peripheral afferent input is sufficient in the absence of supraspinal control to drive the rhythmicity of the pattern (Zehr, 2005). Afferent input comes in the form of cutaneous feedback, vibratory sense, proprioception, load, and muscle stretch and provides information to assist in modulating the behavior (Nielsen, 2003). Within the CPG, there likely exists a complex pool of interneurons that assist in shaping the behavior, and it has been hypothesized that perhaps a single pattern generator may exist for a variety of rhythmic activities such as walking, biking, or swimming that is modulated by the interneuron pool.(Zehr, 2005) Incorporating knowledge

from animal models and the theory of CPGs, Barbeau first described training on a treadmill with body-weight support in humans in 1987 (Barbeau et al., 1987). Reviews of the existing studies are available in the literature and describe the theoretic framework associated with LT (Barbeau et al., 2006; Dietz and Harkema, 2004), describing it as "one of the evidence-based clinical approaches that will be used in the 21st century to enhance recovery of posture and locomotion in stroke, SCI subjects and in many other neurological conditions" (Barbeau, 2003b). These studies illustrate the increasing understanding that training of the spinal cord is dependent on optimal stimulation of "the necessary afferent inputs needed to train spinal circuits responsible for producing desired rhythmic motor patters such as walking" (Dromerick et al., 2006).

Human walking is an incredibly complex task involving a multitude of degrees of freedom and an immense number of combinations of muscle activity. While it is perhaps staggering to consider that the brain can voluntarily control all of these variables during a cyclic, rhythmical task, definitive studies of the spinal control of walking in humans are difficult to conduct due to the inability to directly assay the human central nervous system. In addition, modifications that humans must make for the demands of upright bipedalism make direct translation from studies of quadruped CPGs exceedingly problematic (Nielsen, 2003). As Nielsen stated in a recent review of the central control of muscle activity during walking, "it is the task of the whole central nervous system to generate this muscle activity, to ensure that it is optimally coordinated, to ensure that it is adjusted to the immediate environment, and to modify it when required (Figure 1-2)" (Nielsen, 2003). Nielsen concludes by saying that there is "no reason" to suggest that human walking is controlled exclusively by the spinal cord, nor is there a reason to imply that the motor cortex alone is responsible for activation of muscles during walking. Instead, this activity

related to walking must rely on an integration of spinal neuronal circuitry, afferent signals and descending motor commands (Nielsen, 2003).

This complex integration of motor control requires increased complexity of assessment tools to distinguish true recovery and response to neuroplastic-based interventions. Clinical examinations, however, continue to rely on non-task specific, voluntary activation of movement patterns to describe motor control post stroke, and it is suggested that these current clinical measures may be insufficient. The purpose of the second study of this dissertation is to quantitatively analyze if the FM-LE examination adequately assesses post-stroke motor control relative to walking, or if additional assessment tools are required to capture this integrated capacity of the human nervous system to produce motor control required for walking. As a post-hoc analysis, we will examine additional methods of assessing spinally modulated control of walking and relate both assessments to performance in clinical and biomechanical measures of walking performance.

Examination of Spinal Cutaneous Reflexes

The term "reflex" has often been used to describe distinct, stereotyped motion in response to fixed peripheral nerve stimulations. However, recent research has illustrated that the "connotation that reflexes are stereotyped and immutable is patently false" (Zehr and Stein, 1999). Reflexes, including those elicited from peripheral cutaneous afferents from skin mechanoreceptors, demonstrate task, phase, and intensity dependence for modulation of reflex amplitude. Perhaps the best working definition of a reflex is "a response evoked with great probability by particular stimuli" (Brooks, 1986). The purpose of this section is to introduce the spinal cutaneous reflex by describing its modulations, effect on walking performance, and usefulness in assessing activity-dependent neuroplasticity.

Task Dependency of Cutaneous Reflexes

Early human studies of cutaneous reflexes demonstrated that sub-noxious stimulation of cutaneous nerves resulted in alterations in muscle spindle firing rates without changes in motor neuron firing rates, a result that was only seen when in a standing position (Aniss et al., 1990). Burke et al later discovered inhibitions of the tibialis anterior, soleus, biceps femoris, and vastus lateralis within 100 ms of a stimulus, but only when the muscles were activated. Additionally, the early latency reflexes (60-80 ms) were modulated differently depending on the stability of the posture (sitting, standing, and perturbed standing), finding increased amplitudes with more unstable postures (Burke et al., 1991). Furthermore, positional changes may not only alter the magnitude of the response, but also may reverse the role. For example, stimulation of the posterior tibial nerve in standing inhibits the soleus reflex, while the same reflex is stimulated while prone. Interestingly, the prone response reverses to suppression if a pressure is applied to the sole of the foot, indicating the importance of load receptors and cutaneous input to the sole of the foot in reflex modulation (Abbruzzese et al., 1996).

Phase Dependency of Cutaneous Reflexes

As in the prone versus standing example above, cutaneous reflex responses may change role from suppression to excitation or vice versa depending on the phase of the gait cycle during which the stimulation was applied (De Serres et al., 1995; Duysens et al., 1992; Yang and Stein, 1990). The phenomenon is known as a reflex reversal and can be seen in Figure 3. For example, in the tibialis anterior, stimulation during swing produces an excitatory response while a similar stimulation produces an inhibitory response in the swing to stance transition (Figure 1-3). DeSerres et al. utilized single motor unit analyses to determine that reflex reversals were likely due to competing parallel interneuronal pathways to the alpha motor neuron and that the reflex pathway depended on the phase dependent route through available interneurons (Figure 1-4) (De

Serres et al., 1995). Typically, these reflex reversals are only witnessed in muscles such as the tibialis anterior and biceps femoris that have two patterns of EMG bursting during the course of the gait cycle when stimulating nerves that are predominantly cutaneous (Stein, 1991).

Functional Role of Cutaneous Reflexes during Walking

Cutaneous reflexes appear to have a functional significance of a stumbling corrective response, which has been documented in cats (Drew and Rossignol, 1987; Forssberg, 1979) as well as humans (Zehr et al., 1997). Specifically, Duysens first observed kinematic alterations in ankle dorsiflexion in humans as a result of the swing phase excitatory modulation, but instead of attributing the response to a stumbling corrective response, concluded that the responses are instead related to the opening and closing of reflex pathways to a central pattern generator used in human locomotion (Duysens et al., 1992). Zehr later performed a more extensive analysis of the kinematics of human walking and demonstrated correlations to knee flexion during early swing, ankle dorsiflexion in late stance, and ankle plantarflexion during late swing (Zehr et al., 1997). These movement patterns are all consistent with prevention of tripping, promotion of smooth transition of the swing limb, and preparation for early weight acceptance (Zehr et al., 1997). It has been hypothesized that the cutaneous reflex is most predominant in both stance to swing and swing to stance transitions and acts with other reflexes to maintain stability during active movement (Zehr and Stein, 1999). In a subsequent study, those with post-stroke hemiparesis demonstrated reflex modulation, although the predominant pattern was inhibition, and these reflexes failed to correlate with kinematic responses in the same manner as healthy controls (Zehr et al., 1998). It should be noted, however, that mechanical alterations such as increased joint stiffness may have contributed to the lack of kinematic correlations in those with stroke. In spinal cord injury, reflex modulation was also maintained, and differed from healthy controls in that the predominant response was excitatory (Jones and Yang, 1994). Kinematic

correlations were not performed in this study, but excessive excitation may explain many of the gait abnormalities seen in those with spastic gait patterns after spinal cord injury. At this point, it is unclear if cutaneous reflexes maintain their functional significance in those with central nervous system injury.

Role of Reflexes in Study of Activity Dependent Neuroplasticity

Presently, a great opportunity exists to develop studies investigating the potential of the human nervous system to modify reflexes as a result of activity-dependent rehabilitation in those with central nervous system injuries. While H-reflex modulation has been studied as a result of locomotor rehabilitation post spinal cord injury (Trimble et al., 2001; Trimble et al., 1998), investigators have not yet utilized the potential of examining multisynaptic cutaneous reflex modulation in this population. Similarly, cutaneous reflexes have been minimally studied in the stroke population, and current activity based therapies create a need to understand the alteration of cutaneous reflexes as the result of an intervention. However, a single study was recently completed in the spinalized cat model undergoing locomotor training (Cote and Gossard, 2004). In this study, 10 of the 71 pathways studied demonstrated some degree of post-training modulation. Six of these 10 pathways involved the medial plantar nerve, which innervates the plantar surface of the foot, indicating that ground contact may play an important role in the modulation of the reflexes (Cote and Gossard, 2004). Figure 1-5 illustrates an example of a medial gastroc motoneuron and the reduction of inhibition that is seen as a response post locomotor training (Figure 1-5). This study demonstrates promise for cutaneous reflex modulation post nervous system lesion and provides a rational for study in the human population.

Conclusion

In summary, the following experiments allow the possibility of examining individuals post-stroke during the functional activity of walking in an effort to measure elements of recovery at the activity level. Biomechanical patterning in ground reaction force generation, analysis of EMG patterning, and spinal level reflex modulation may all reflect ways in which individuals post-stroke achieve the behavior of walking. These assessment tools, while computationally intensive, may provide preliminary evidence of the ability to distinguish recovery from compensatory adaptation at an activity level. These measurement tools could therefore serve as a framework by which clinical analogs could be developed to improve clinicians' ability to optimize clinical decision making and interpret intervention efficacy.

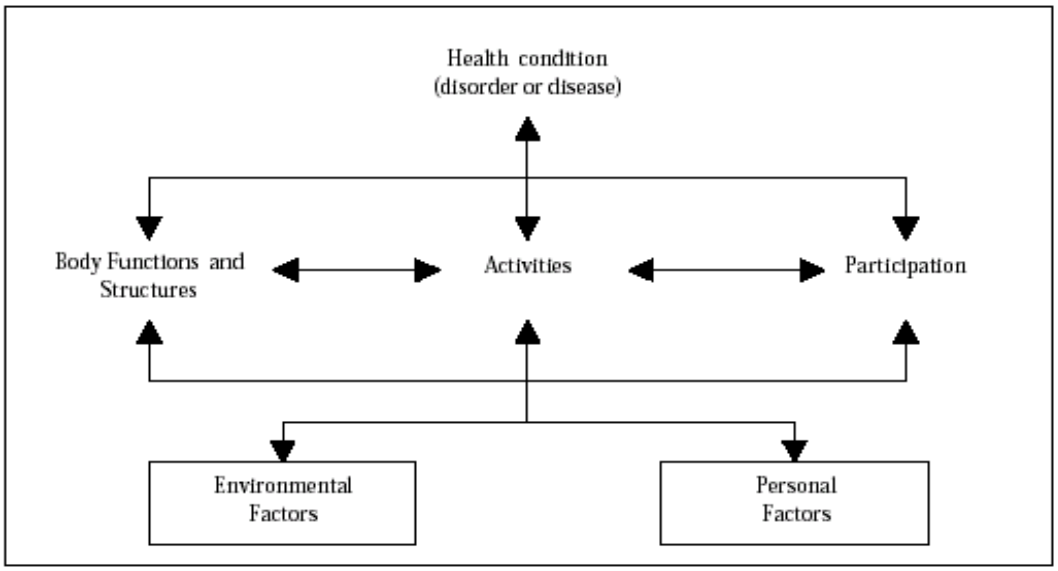

Figure 1-1. ICF model of rehabilitation.

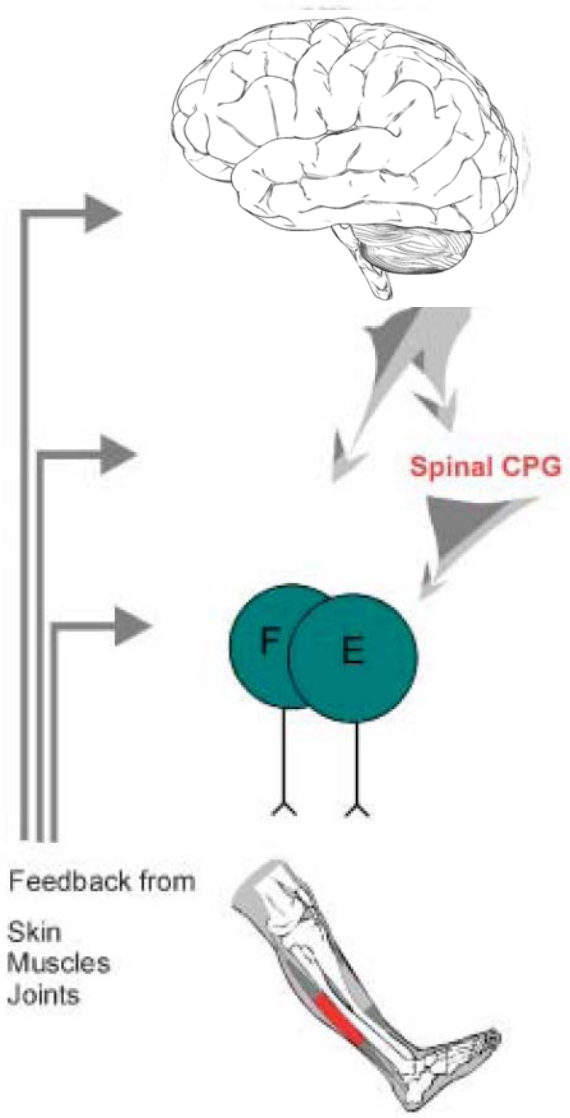

Figure 1-2. Central control centers for control of walking. (from Nielsen JB. How we walk: central control of muscle activity during human walking. *Neuroscientist.* Jun 2003;9(3):195-204.) Muscle activation comes directly from the cortex as well as spinal CPGs and is modulated at each location by afferent input.

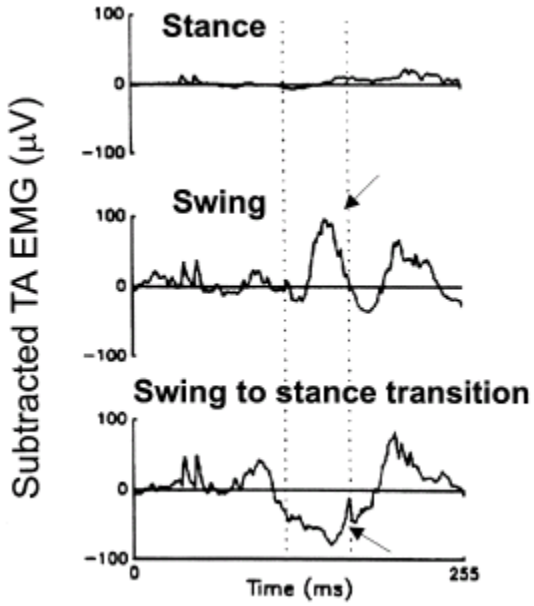

Figure 1-3. Reflex reversal. (from Zehr EP, Stein RB. What functions do reflexes serve during human locomotion? *Prog Neurobiol.* Jun 1999;58(2):185-205.) Notice the lack of response during stance but a switch from excitation to inhibition in the middle latency going from swing to stance initiation.

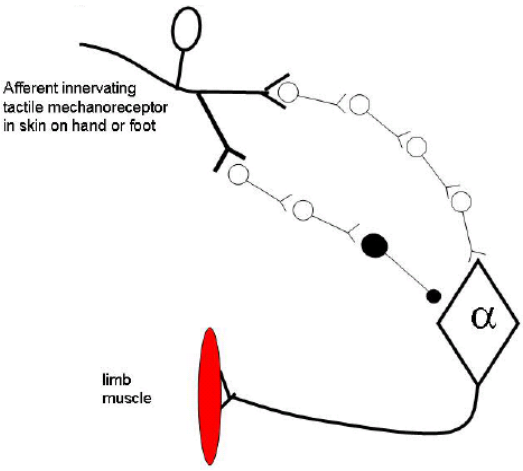

Figure 1-4. Afferent signaling to reflex interneurons. (From Zehr EP. Training-induced adaptive plasticity in human somatosensory reflex pathways. J Appl Physiol 2006; 101: 1783-94.) Reflex reversals may be due to competing interneuronal pathways to the alpha motor neuron.

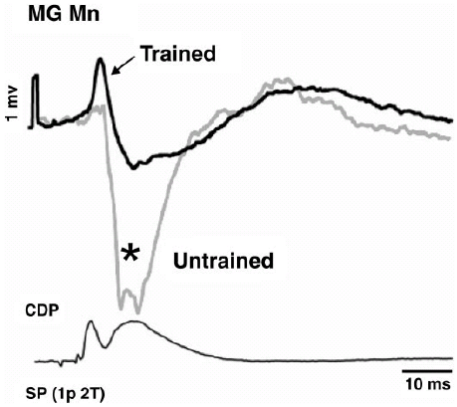

Figure 1-5. Post training modulation of cutaneous reflexes in spinalized cats. (From Cote MP, Gossard JP. Step training-dependent plasticity in spinal cutaneous pathways. J Neurosci 2004; 24: 11317-27.) Note the early latency excitation and later latency decrease of inhibition.

CHAPTER 2
ANTERIOR-POSTERIOR GROUND REACTION FORCES AS A MEASURE OF PARETIC LEG CONTRIBUTION IN HEMIPARETIC WALKING

Introduction

Post-stroke hemiparesis results in a unilateral primary impairment of the paretic leg that results in a disrupted walking pattern. Therapeutic strategies for walking recovery have largely focused on the paretic leg, as it exhibits a reduced muscular output, which is evidenced by decreased maximal voluntary contraction (Mulroy et al., 2003), reduced EMG amplitudes during walking (Knutsson, 1981), and a decline in mechanical work performed (Olney et al., 1991). However, there are limitations in available quantitative measures of strength (they are not specific to the walking task), EMG (it is difficult to synthesize information from multiple muscles) and mechanical work (e.g., requires multiple assumptions (Aleshinsky, 1986)) such that currently available measures give an incomplete assessment of the coordinated output of the paretic leg during walking. Walking speed is the most widely used measure of performance; however, compensatory action by the non-paretic leg can result in a relatively functional walking speed despite poor coordination of the paretic leg. While a training program may increase one's walking speed by making a compensatory strategy more effective, current neurorehabilitation philosophies based on the principles of neuroplasticity are directed at the restitution of neurological deficits. Thus, a quantitative measure of the coordinated output of the paretic leg might predict the outcome of therapy; assist in evaluating the specific muscle coordination changes associated with various therapeutic interventions; and correlate with structural and functional studies of the nervous system such that the underlying mechanisms can be better understood.

Olney et al (1991) suggested that the paretic leg, regardless of hemiparetic severity, performs approximately 40% of the mechanical work of walking, as calculated from kinetic

analyses based on intersegmental joint powers (Olney et al., 1991). These mechanical work estimates, however, rely on assumptions as to the recovery of mechanical work from individual sources and intercompensation between sources (Aleshinsky, 1986), and do not describe what functional tasks are being accomplished by the work. Forward dynamic simulation models have demonstrated that more of the mechanical work performed during a gait cycle is done in early single leg stance in order to raise the body's COM than occurs in double limb support (DLS) prior to swing, which primarily provides forward propulsion and swing initiation.(Neptune et al., 2003) The power produced during DLS likely decreases even more in those with slower walking speeds, implying that an even higher proportion of work is done to raise the COM. Currently, no adequate measure exists to examine the paretic leg contributions to the task of propelling the body forward during walking, which is an essential requirement of locomotion (Shumway-Cook and Woollacott, 2001).

Paretic limb work production has previously been studied utilizing a well-controlled pedaling paradigm (Kautz and Brown, 1998; Kautz and Patten, 2005). This model has shown that the paretic leg produces significantly less mechanical work output than do healthy, age-matched controls (Brown and Kautz, 1999). This net decrease in mechanical work output is a product of less positive work and more negative work being done by the paretic leg (Brown and Kautz, 1999). Of particular interest is that the pedaling-derived measures of mechanical work seem to assess coordinated output independent of the need to support the body by providing postural stability as a result of the seated posture. As a result, the contribution of the paretic leg to the pedaling task in the most impaired subjects was found to be near zero, or even negative (i.e., hindering task accomplishment that requires additional work done by the non-paretic leg).

Thus in contrast to the findings of Olney et al. (1991) in walking, we were able to link hemiparetic severity to motor performance (Brown and Kautz, 1999).

Similarly, the anterior-posterior ground reaction forces (A-P GRFs) may represent an appropriate method of measuring the contribution of the paretic leg to the coordinated task of forward propulsion during walking. Previous studies have implemented A-P GRF as a measure of the forward propulsion and braking in people with hemiparesis utilizing a cane for ambulatory assistance (Chen et al., 2001), but the A-P GRFs have not been utilized as a measure of the mechanical contribution of the paretic and non-paretic legs. In addition, we propose comparing the paretic leg coordinated output in walking to our previously derived measures for pedaling and propose that pedaling measures will provide confirming evidence of the importance and robustness of these walking measures. Specifically, we hypothesize that measures derived from the A-P GRF impulse (paretic and non-paretic propulsive impulse, paretic and non-paretic braking impulse, and paretic net propulsion) will correlate with gait speed, hemiparetic severity, and the positive and negative work measurements in pedaling.

Methods

The A-P GRF data presented in this study were collected (but not reported) as part of a larger study that investigated the links between gait characteristics and bone density in chronic stroke survivors (Worthen et al., 2005).

Participants

Individuals presenting with chronic stroke were recruited for this study at the Palo Alto Department of Veterans Affairs Medical Center. Forty-seven individuals with chronic hemiparesis (41 male, 6 female; ages = 62.4 ± 10.2 (SD) years; time since stroke (yrs) = 4.3 ± 3.8; affected side: left = 25, right = 22) participated in the study. A subset of this population also

participated in a pedaling study in our lab (Kautz et al., 2003). This sample of 16 included 14 male, 2 female; 9 with left hemiparesis, 7 with right hemiparesis; average age of 63.5 $\pm$ 6.6 years; average chronicity was 3.0 $\pm$ 1.4 years. Written informed consent was obtained from all participants for each study and the Stanford University Administrative Panel on Human Subjects in Medical Research approved both protocols.

Inclusion criteria included the following: unilateral weakness; less than 85 years of age; time since stroke greater than 12 months; if female, at least 5 years past the onset of menopause; and ability to walk 10 meters in 50 seconds or less without contact assistance. Exclusion criteria included the following: more than 1 previous cerebral vascular incident; inability to provide informed consent; use of osteoporosis drug or hormone replacement therapy within the past 5 years; history of leg fracture or pain; and the existence of any other medical condition that could affect bone mass.

Participants were characterized according to their level of hemiparetic severity, identified on the basis of the Brunnstrom motor recovery stages (Brunnstrom, 1966). These participants demonstrated a range of abilities to perform movements within and outside of extensor and flexor synergy patterns (Brunnstrom, 1966). Severe hemiparesis was defined as subjects rated as Brunnstrom stage 3 (n=19), moderate hemiparesis was defined as subjects rated as either a Brunnstrom stage 4 or 5 (n=18), and mild hemiparesis was defined as subjects rated Brunnstrom stage 6 (n=10).

Variables

Walking speeds were measured while each participant walked on a 4.3 meter long GAITRite portable walkway system (CIR Systems, Inc). Additionally, GRF were measured throughout the stance phase for both the paretic and non-paretic legs as each participant walked at their self-selected speed along a 10-meter walkway equipped with embedded force platforms

(Advanced Medical Technology, Inc and Bertec). GRF data were acquired at 200 Hz and were filtered with a lowpass fourth order Butterworth filter at 20 Hz forward and backward in time. The A-P GRF component (normalized by each individual's body weight) was used in the subsequent analysis. Four to fifteen trials were collected in order to assure adequate contact on the force platforms to determine the GRF and walking speed for each participant. When possible, multiple foot contacts were averaged to generate GRF values, but in one participant, only one trial could be analyzed due to inconsistent foot striking on the force plate.

A subset of the sample also participated in a separate experiment in which they were assessed on a cycle-ergometer to evaluate work production generated by each leg. The positive, negative, and total work (sum of positive and negative) were calculated for each lower extremity. The pedaling evaluations were completed with a custom two-servomotor ergometer, which has been described previously in the literature (Kautz and Patten, 2005). In the present pedaling trials, the servomotors were programmed to emulate conventional two-legged pedaling, and toe clips were utilized to allow the hip flexors to generate power during the cycle.

The stance phase was separated into four bins in order to analyze impulse generation at various time points in the gait cycle: 1) double limb support after paretic foot strike, 2) the first 50% of paretic single limb stance, 3) the second 50% of paretic single limb stance, and 4) double limb support prior to paretic swing. Customized Matlab programs were written to process the data, and when possible raw data from two consecutive heel strikes were analyzed to examine the temporal relationship with the contralateral leg. When consecutive heel strikes were not collected, average temporal relationships were assumed to be representative of a subject's gait.

Variables derived from the A-P GRF were defined as follows: 1) propulsive impulse is the time integral of the positive A-P GRF, 2) braking impulse is the time integral of the negative A-P

GRF, and 3) net impulse is the sum of the propulsive impulse plus the braking impulse for each leg. Propulsive and braking impulses were also calculated within each bin. The percentage of total propulsion generated by the paretic leg, referred to as paretic propulsion (Pp), was calculated by dividing the propulsive impulse of the paretic leg by the sum of the paretic and non-paretic propulsive impulses.

Statistical Analysis

Correlations between parametric variables were analyzed using Pearson's correlation coefficient, while correlations with hemiparetic severity levels were performed using the non-parametric Spearman's correlation. All statistics were run using SPSS version 11.0 (SPSS, Inc.).

Results

Gait Characteristics

Figure 2-1 illustrates the A-P GRF tracing for three representative participants. In steady state (constant speed) walking, the area under the curve in the positive direction (propulsion) should roughly equal the area under the curve in the negative direction (braking) and the two leg's tracings should be similar in shape and magnitude. Note that is the top participant, the paretic and non-paretic legs were fairly symmetrical. However, the more impaired subjects were asymmetrical. In order to maintain steady state walking speeds, reduced net propulsion by the paretic leg has to be offset by increased propulsion in the non-paretic leg. As the graphs progress from mild to severe hemiparesis, a smaller percentage of total propulsion was generated by the paretic leg (P_P), corresponding with a slower walking speed.

Walking speed. Walking speed was positively correlated with paretic propulsive impulse, non-paretic braking impulse, paretic net impulse, non-paretic net impulse, and the net impulse of Bin4 on the paretic leg (Table 2-1).

Hemiparetic severity. Severity was significantly correlated with propulsive impulse, net impulse, and bin4 net impulse in the paretic leg, and propulsive impulse, braking impulse, and net impulse in the non-paretic leg (Table 2-1).

Analyses then examined the effect of hemiparetic severity on P_P. Figure 2-2 illustrates that for those categorized as mild severity, the mean P_P is approximately 49%. Those participants who demonstrated moderate severity had a mean P_P of 36%, whereas those participants with severe hemiparesis had a mean P_P of only 16%.

All of the participants in this study were allowed to walk with the assistive and/or orthotic device that they normally use in everyday walking. Eight of 19 participants with severe hemiparesis used an ankle-foot orthosis (AFO), and 11 of the 19 used some form of unilateral assistive device. Analyses were done to see if orthotic and/or assistive device usage affected the P_P. There was not a significant difference ($p=0.176$) between those that used an AFO ($P_P=12.07\%$) and those who did not ($P_P=19.32\%$). There was a non-significant difference ($p=0.74$) between those using assistive devices ($P_P=12.45\%$) and those who did not ($P_P=21.52\%$). Those participants who used neither an AFO nor an assistive device had a P_P of 21.14%.

P_P was significantly correlated with both speed ($r=0.551$, $p=0.000$) and with hemiparetic severity ($r=0.737$, $p=0.000$). Note, however, that five individuals with severe hemiparesis walked faster than the functionally significant 0.8 m/s(Perry et al., 1995b) and all had $P_P \leq 25\%$ (Figure 2-3). Additionally, three individuals with mild severity walked more slowly than 0.8 m/s and all had $P_P \geq 49\%$. These eight participants are indicated in Figure 2-3 with filled markers.

Pedaling Characteristics

Pedaling subset. Sixteen individuals completed the full pedaling and gait evaluations, including work and force production results.

Correlations of pedaling and walking. Measurements of work production in pedaling (total work, positive work, and negative work) were correlated with the impulse generated during walking (paretic propulsive impulse, paretic braking impulse, paretic net impulse, and paretic net Bin4 impulse) (Table 2-2).

Correlations of pedaling and walking with hemiparetic severity. Hemiparetic severity was positively correlated with total work done in pedaling ($r=0.798$, $p=0.000$), with positive work done in pedaling ($r=0.588$, $p=0.017$), and negative work done in pedaling ($r=0.791$, $p=0.000$).

Discussion

P_P was found to provide a quantitative measure of the coordinated output of the paretic leg that is sensitive to hemiparetic severity. The correlation between P_P and hemiparetic severity was strong and there was a dramatic difference between those with severe hemiparesis (16% P_P) and a mild hemiparesis (49% P_P). These findings demonstrate that Pp levels are sensitive to hemiparetic severity, differing from mechanical work estimates that calculate work at a constant 40% regardless of severity (Olney et al., 1991). Reduced P_P by those with severe hemiparesis does not seem to be attributable solely to the use of an assistive and/or orthotic device, as even those with severe hemiparesis not using assistive and/or orthotic devices demonstrated markedly reduced Pp (21.14%). In addition to P_P, the raw measures of walking presented, i.e. paretic propulsive impulse, net paretic impulse, and net impulse in Bin4 are all sensitive to the severity of the hemiparesis, implying that the A-P GRF quantities are appropriate measures for assessing the paretic leg contribution to walking that are sensitive to severity. Additionally, these results also corroborate previous findings correlating hemiparetic severity with the pedaling measures.

The overall aim of this paper was to further our understanding of the contribution of the paretic leg to forward propulsion in hemiparetic walking. Previous work on hemiparetic

interlimb coordination and contributions to total work using a pedaling paradigm has indicated that work measurements are sensitive to hemiparetic severity (Kautz and Brown, 1998). Specifically, those with more severe hemiparesis produce less total work and encounter more resistance from the paretic limb than do those with less severe hemiparesis. Comparing A-P GRF to pedaling work, we see some similarities in the task of walking as both total and positive work strongly correlate with propulsive impulse, net paretic impulse, and net impulse generated during Bin4, which is the most propulsive phase of the gait cycle (Neptune et al., 2001).

It is important to realize that, in addition to the active generation of propulsive forces by muscles, there were also direct mechanical influences associated with the value of Pp achieved because of the expected strong relationship between foot placement and amount of propulsive impulse. If the leg were to act purely as a rigid strut (i.e., GRF vector parallel to long axis of leg), as in an idealized inverted pendulum, the A-P GRF would be directly related to the position of the foot relative to the body's COM (i.e., anterior foot position produces posterior GRF, the posterior foot position produces an anterior force, and asymmetry between the percent of the stance phase with the foot anterior versus posterior would introduce a similar asymmetry in propulsive impulse). Thus, reduced propulsion in Bin4 is likely related to an inability to achieve adequate hip extension (e.g., sufficiently posterior foot position) in addition to reduced active generation of propulsive GRF by the muscle forces. Note that the resistive impulse late in Bin4 that follows the generation of some propulsive impulse (Figure 2-1, bottom tracing) is unlikely to be related to the direct mechanics as the foot is likely behind the COM in this phase. Consequently, direct mechanical effects are not sufficient to explain Pp. In addition, the biomechanics underlie one of the differences between walking and the pedaling paradigm.

Negative work in pedaling is likely due to resistance from the paretic leg, while braking in walking may be a mechanical response to having taken a longer stride with the paretic leg.

Strong correlations were seen with net impulse (e.g., propulsion – resistance) in Bin4, the double limb support prior to the swing of the paretic limb. Bin4 is important in the attainment of speed during walking, and DeQuervain illustrated that those with hemiparesis with the slowest gait velocity spend the most time in Bin4 (De Quervain et al., 1996). This phase may be of particular importance in the act of progressing the body forwards as it coincides with the burst of ankle power (Olney et al., 1991), much of which is stored mechanical energy from gastrocnemius and soleus activity and acts to propel the body forwards (Neptune et al., 2001). Both total work and positive work performed during pedaling showed the strongest correlation with GRF impulses in Bin4 and this phase also had the strongest correlation with hemiparetic severity.

Lastly, it may be possible to utilize the P_P to document compensatory gait patterns. For example, 5 of those with a severe hemiparesis had a walking speed greater than 0.8 m/s, but had a P_P of $\leq$ 25%, implying that they were achieving their velocity through some mechanism other than paretic leg contribution. These compensations to achieve functional velocities are not appreciated when examining walking speed alone, but may be important in assessing outcomes for a therapeutic intervention. A training program may increase one's walking speed by only making a compensatory strategy more effective, but current neurorehabilitation philosophies based on the principles of neuroplasticity are directed at the restitution of neurological deficits. Thus, P_P may be an effective tool in distinguishing functional compensation from physiological restitution.

Table 2-1. Correlations of gait characteristics with walking speed and stroke severity

Outcome Measure	**Walking Speed** [*]		**Hemiparetic Severity** [#]	
Paretic Propulsive Impulse	**r= 0.641**	**p=0.000**	**r=-0.650**	**p=0.000**
Paretic Braking Impulse	r=-0.235	p=0.112	r=-0.162	p=0.276
Non-Paretic Propulsive Impulse	r= 0.140	p=0.350	**r= 0.467**	**p=0.001**
Non-Paretic Braking Impulse	**r= 0.696**	**p=0.000**	**r= 0.507**	**p=0.000**
Paretic Net Impulse	**r= 0.363**	**p=0.012**	**r=-0.659**	**p=0.000**
Non-Paretic Net Impulse	**r=-0.431**	**p=0.002**	**r= 0.753**	**p=0.000**
Paretic Bin4 Net Impulse	**r= 0.748**	**p=0.000**	**p=-0.681**	**p=0.000**

[*]Pearson Correlation Coefficient, [#]Spearman Correlation Coefficient

Table 2-2. Walking and pedaling correlations

Paretic LE: Pedaling	**Paretic LE: Walking**	**r**	**Sig.**
	Propulsive Impulse	**0.588**	**0.017**
Total Work	Net Paretic Impulse	**0.550**	**0.027**
	Net Bin4 Impulse	**0.748**	**0.001**
	Propulsive Impulse	**0.613**	**0.012**
Positive Work	Net Paretic Impulse	**0.631**	**0.009**
	Net Bin4 Impulse	**0.661**	**0.005**
Negative Work	Braking Impulse	0.064	0.813

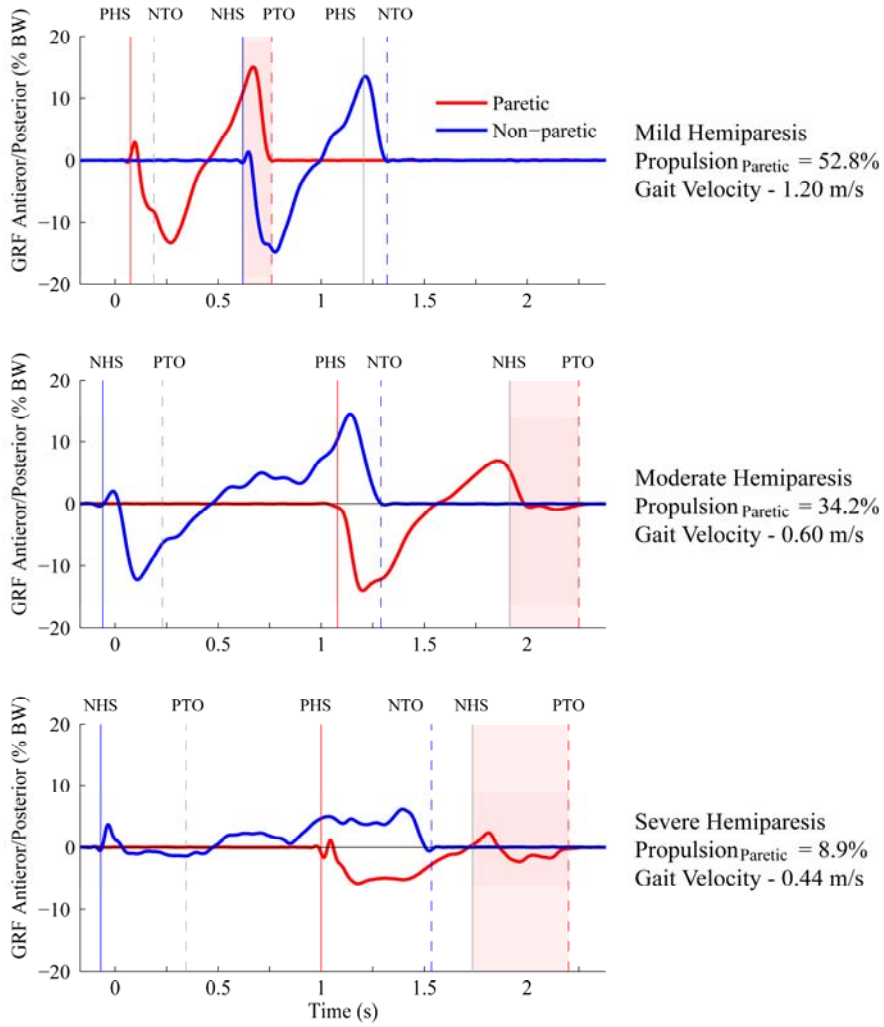

Figure 2-1. Comparison of the anterior-posterior ground reaction forces for the paretic (red lines) and non-paretic legs (blue lines) of subjects of differing hemiparetic severity. Positive values represent propulsion, and the positive area under the curve is the propulsive impulse. PHS = paretic heel strike, NTO = non-paretic toe off, NHS = non-paretic heel strike, and PTO = paretic toe off. Increased hemiparetic severity was associated with decreased PP and decreases in self-selected walking speed.

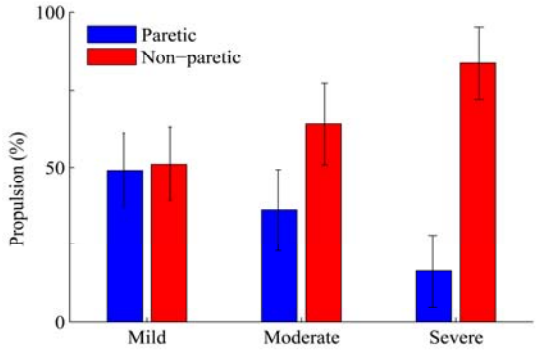

Figure 2-2. Comparison of the average propulsion (expressed as a percent of the total propulsion) generated by the paretic (blue bars, note that this is defined as Pp) and non-paretic legs (red bars) of subjects of differing hemiparetic severity. There are substantial differences in the percent of total propulsion generated by the paretic leg (PP) in those with severe and moderately severe hemiparesis when compared with those with mild severity. Compensation by the non-paretic leg is noticeable in the asymmetry shown by the moderate and severe groups. Error bars indicate standard deviation for each variable.

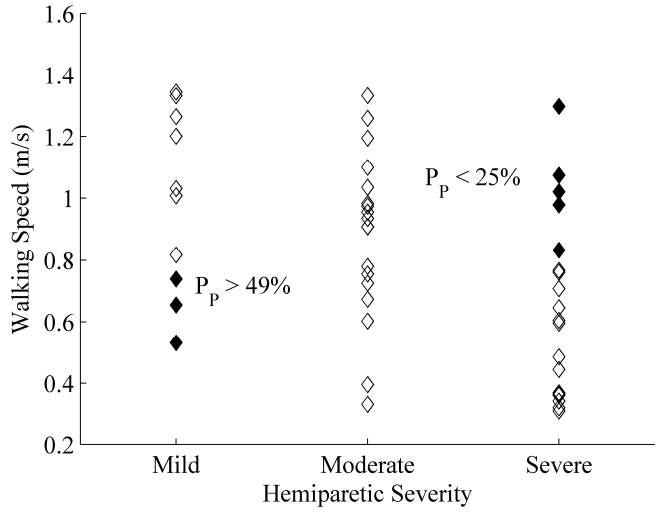

Figure 2-3. Individual walking speed data for subjects in each of the hemiparetic severity groups. While there is a weak overall trend for walking speed to decrease with severity, the variability is substantial and the speed ranges in each of the groups overlap substantially. Five participants with severe hemiparesis are still able to achieve normal walking speeds (>0.8 m/s), but all demonstrate substantial decreases in PP. Conversely, 3 participants with mild hemiparesis walked <0.8 but have normal PP (> 49%). These eight participants are indicated with filled markers.

CHAPTER 3
EVALUATION OF ABNORMAL SYNERGY PATTERNS POST-STROKE: RELATIONSHIP OF CLINICAL EXAMINATION TO HEMIPARETIC LOCOMOTION

Introduction

Motor recovery post-stroke is difficult to measure, and theories surrounding motor function post-stroke have been dominated by the concept of progressing through predictable stages of recovery (Brunnstrom, 1966; Twitchell, 1951). This progression is based on the organization of reflex behavior, theorizing that severe impairments reflect a return to previously assimilated primitive reflexes. According to this theory, primitive motor pathways accessible by reflex activation provide a foundation for more complicated voluntary movements (Fugl-Meyer et al., 1975) and someone with non-flaccid hemiparesis (preservation of reflexes with no voluntary movement) would present with a recovery of motor function in a regular sequence in which initial voluntary movements are dependent on primitive motor pathways and synergistic movements. Patients fully recovering from stroke are thought to gradually develop more complex motor behaviors, fully integrating voluntary movement patterns outside of stereotypical abnormal synergy patterns (Brunnstrom, 1966). Based on this theory, Fugl-Meyer in 1975 developed a measurement instrument reflecting this hierarchy of the emergence of complex motor control behaviors in order to quantify recovery of motor function post-stroke (Fugl-Meyer et al., 1975). This instrument is divided into upper extremity and lower extremity components focusing on distinct constructs such as reflexes, voluntary control of isolated movement, coordination and speed, with an additional section specific to balance recovery (Fugl-Meyer et al., 1975). Specifically, the lower extremity motor evaluation (FM-LE) consists of a total score of 34 points with 17 items scored on a 0-2 scale.

Since its inception, the FM-LE has been studied extensively to document stroke-related motor impairment and recovery. The FM-LE exam has undergone scrutiny via reliability and

validity studies (Duncan et al., 1983; Fugl-Meyer et al., 1975), and has been used to validate other instruments (Lamontagne et al., 2001; Wang et al., 2002). Furthermore, the FM-LE has been utilized to measure the efficacy of novel therapeutic approaches (Dobkin et al., 2004), and has been included in models attempting to predict functional recovery (Kollen et al., 2005; Nadeau et al., 1999). However, the motor control deficits that the FM measures may differ from deficits seen during activities such as walking. Walking is a task specific activity that is at least partially controlled by spinal cord level automaticity via the presence of a complex system of spinal interneurons, or central pattern generator (CPG) (Barbeau, 2003a; Dietz and Harkema, 2004; Edgerton et al., 2004). The CPG has been proposed to act in concert with both peripheral afferent input and supraspinal control to produce functional and coordinated walking behavior (Nielsen, 2003; Yang and Gorassini, 2006; Zehr, 2005). As such, evaluation of voluntary motor impairment using FM-LE may have limited ability to measure the neural determinants of walking dysfunction. In particular, control of isolated voluntary force and movement differs markedly from the cyclical patterns of walking, which rely heavily on spinal circuits and sensorimotor integration.

Recent advancements have been made in the use of EMG factorization procedures to identify shared patterns of activation among groups of muscles. Such approaches are consistent with the historical clinical perspective of functional muscle groupings, but allow more objective determination of muscle groupings under any movement condition including complex functional activities. Ivanenko et al. have used a principal component analysis to identify five basic underlying factors that explain 90% of the variance of muscle EMG during gait activities that are modulated by both descending and proprioceptive signals (Ivanenko et al., 2004). Using jumping, swimming, and walking patterns of frogs, d'Avella and Bizzi utilized EMG recordings

to identify a mixture of synergies that may be isolated or shared to account for all of the movement variability (d'Avella et al., 2003). This control is speculated as being downstream of the processes that generate motor activation (i.e. cortical inputs) (Ivanenko et al., 2006). Using microstimulation, iontophoresis, and behavioral analysis, Bizzi et al. localized this modular organization at the level of the spinal cord, and defined the ability to generate a specific pattern of motor output with a specific pattern of input into these spinal modules (Bizzi et al., 2008). Additionally, non-negative matrix factorization (NNMF) analysis has demonstrated that these synergistic activation patterns produce previously reported stereotypical responses to postural perturbations to promote balance equilibrium (Ting and Macpherson, 2005; Torres-Oviedo and Ting, 2007). Recent work in our laboratory has utilized the NNMF to identify the number and composition of EMG modules (NNMF factors) accounting for lower extremity EMG during walking in healthy adults and adults post-stroke (Clark et al., 2008). Emergence of these patterns post-stroke may reflect an emergence of complex behavior and neuromotor organization during the task of walking that cannot be identified during isolated single and multi-joint movements.

The purpose of this study is to test whether the motor impairment measured by the FM-LE is indicative of motor dysfunction during walking in adults with post-stroke hemiparesis. Specifically, we hypothesize that the FM-LE and FM-S will demonstrate weak correlations with biomechanical and clinical measurements of walking performance. As both the FM-LE and NNMF have been used to probe the underlying neural determinants of motor function, a secondary analysis will be to quantitatively analyze whether these two methods are measuring the same construct. Further, we test whether classification of stroke patients based on each of these approaches yields associations between the level of classification and deficits in walking performance, hypothesizing that NNMF classification will better stratify walking performance.

Methods

Individuals with chronic (greater than six-months post-stroke) hemiparesis participated in a study at the Department of Veterans Affairs (VA) Medical Center in Gainesville, FL. Thirty-four individuals (15 female and 19 male), age 60 + 12.2 years (standard deviation), 13 with right and 21 with left hemiparesis participated in the study. Participants had a history of a single unilateral stroke, were ambulatory without contact assistance, were able to follow a multiple step command, and did not have other medical issues interfering with their ability to walk. In addition, 17 healthy controls (3 male, 14 female, mean age 65.1 $\pm$ 10.7 years) participated in the study and walked at 0.6 m/s to match the average walking speed of the hemiparetic participants. All participants signed written informed consent approved by University of Florida Institutional Review Board/Gainesville VA Subcommittee for Clinical Investigation.

Each participant walked for two 30 second trials on an instrumented treadmill (Techmachine, Andrezieux Boutheon, France), to collect ground reaction forces (GRF) and kinematic data. GRF data were acquired at 200 Hz and were filtered with a low pass fourth order Butterworth filter at 20 Hz forward and backward in time. The A-P GRF component (normalized by each individual's body weight) was used in the subsequent analysis. Surface EMG (Konigsberg Instruments, Pasadena, CA) was acquired using bipolar Ag-AgCl surface electrodes (Vermed, Inc., Bellows Falls, VT) during treadmill walking and the FM-LE from eight different muscles: tibialis anterior (TA); soleus (SOL); gastrocnemius (GAS); vastus medialis (VM); rectus femoris (RF); biceps femoris (BF); semimembranosus (SM), and gluteus medius (GM). Reference electrodes were place over the electrically neutral patella. EMG signals were filtered with a 40Hz high pass filter and then a 20Hz low pass filter for averaging multiple steps of walking data or a 4Hz low pass filter to smooth one-trial data for the subsequent FM-LE analysis.

FM-LE Stratification

Each participant was stratified by severity according to 22-point sub-section of the FM-LE that examines the ability to perform voluntary isolated movement independent from mass patterns of whole-limb co-activation (FM-S) and excludes the reflex and coordination/speed parameters (severe, n=11; moderate, n=14; mild, n=9) and examined with a battery of walking-specific clinical and biomechanical assessment tools. In this stratification, a FM-S score of $\leq$ 15 characterized severe hemiparesis; 15-19 characterized moderate hemiparesis; and $\geq$ 20 determined mild hemiparesis (Kautz and Patten, 2005). These cutoffs are based on theoretical limitations of moving within abnormal synergy patterns, combining synergy patterns, or moving at least partially outside of the patterns.

Non-negative Matrix Factorization

For each subject, EMG were combined into an m x t matrix (EMGo), where m indicates the number of muscles and t is the time base (t = # of strides x 101). A non-negative matrix factorization algorithm was then applied to this matrix for a set of consecutive gait cycles because inherent stride-to-stride variability contains structured information that is critical to differentiating between independent factors and establishing robust factor definitions. NNMF defined the factors by populating two matrices: 1) an m x n matrix indicating the relative weighting of each muscle within each factor; and 2) an n x t matrix reflecting the activation timing profile of the factor across the gait cycle.

NNMF assumes that the weightings remain fixed over the entire gait cycle, and that muscles may belong to more than one factor. The two matrices were multiplied to produce an *m x t* matrix of reconstructed EMG (EMG_r), which was then compared to the original EMG_o and the agreement quantified by calculating the sum of the squared errors: $(EMG_o – EMG_r)^2$. Within

this framework, NNMF performed an iterative optimization procedure by adjusting the weightings and timings until they converged on factor definitions that minimized the error.

Separate NNMF analyses were performed with the output constrained to 1, 2, 3, 4 and 5 factors. To determine how many factors were actually needed for each leg of each subject, we calculated the variability accounted for ($VAF = 1 - (EMG_o – EMG_r)^2/EMG_o^2$). VAF was calculated for each muscle across the entire gait cycle and for all muscles within each of six phases of the gait cycle (calculated as the cumulative VAF for all muscles within each phase). Beginning with a single factor, if VAF was greater than or equal to 90% for all 14 conditions (8 muscles, 6 phases), then it was concluded that additional factors were not needed. Otherwise, the number of factors was increased until all conditions achieved 90% VAF or until adding an additional factor did not substantially increase VAF for the muscle(s) and/or phase(s) with the lowest VAF.

Clinical and Biomechanical Assessment Tools

Walking speed. Self-selected walking speed overground was measured on an instrumented walkway (GAITRite, CIR Systems, Inc, Havertown, PA).

Berg Balance Test (BBT). The BBT is a 14-item test that requires an individual to perform everyday tasks of increasing difficulty such as sitting, moving from one chair to another, standing up, turning around, picking up an item from the floor, as well as the performance of more challenging tasks such as standing on one foot (Berg et al., 1992a; Berg et al., 1992b).

Dynamic Gait Index (DGI). The DGI rates performance from 0 (poor) to 3 (excellent) on eight different gait tasks, including gait on even surfaces, gait when changing speeds, gait and head turns in a vertical or horizontal direction, stepping over or around obstacles, and gait with pivot turns, and steps (Shumway-Cook and Woollacott, 2001).

Paretic propulsion (Pp). Pp is a quantitative measure of the coordinated output of the paretic leg, which describes the contribution of the paretic leg in propelling the center of mass forward during walking and is defined as the percentage of propulsion performed by the paretic leg.(Bowden et al., 2006) Statistics were run on the absolute deviation from normal (0.5).

Paretic step ratio (PSR). PSR is defined as the percentage of stride length performed by the paretic step (Balasubramanian et al., 2007). Statistics were run on the absolute deviation from normal (0.5).

Paretic pre swing (PPS). The percentage of the gait cycle spent in the double-limb support phase prior the paretic pre-swing (De Quervain et al., 1996).

The gait cycle was divided into six phases for data analysis (Figure 3-1). The percentage of EMG activity in each phase was compared between each FMS severity level and for controls.

Statistical Analysis

Group analyses were completed using a non-parametric Kruskal-Wallis H Test with Rank Sums Tests post-hoc analyses. FM-LE and FMS values as well as the number of NNMF factors explaining EMG variability were correlated to the walking assessment battery using the non-parametric Spearman's correlation coefficient. Significance for all tests was set at alpha < 0.05. All statistics were run using SPSS version 15.0 (SPSS, Inc.).

Results

Of the 34 participants, several demonstrated higher activation of the TA during walking than during isolated dorsiflexion tasks in supine (n=12, 35%), during sitting voluntary dorsiflexion (n=17, 50%), and during standing dorsiflexion (n=18, 53%). An example of this decreased TA activation during isolated tasks is seen in Figure 3-2, in which an individual exhibited no active dorsiflexion during the isolated FM task but demonstrated active DF movement during walking accompanied by discrete bursting of the TA EMG (Figure 3-2). The x

and y scaling for the EMG tracing was kept consistent for the purposes of visual comparison. The accompanying images illustrate the inability to dorsiflex the ankle in item 10.a. and functional dorsiflexion during the walking cycle in item 10.b.

Fugl-Meyer Assessment and EMG Activation Patterns

When stratifying according the FMS severity, five of the six FM-LE tasks show varying degrees of differences between severity levels (Figure 3-3). In the supine extension task, TA ($p=0.046$), MG ($p=0.048$), BF ($p=0.005$), SM ($p=0.001$), and GM ($p=0.008$) demonstrate main effects, and of these BF ($p=0.004$), SM ($p=0.002$), and GM ($p=0.0008$) show significant increases in EMG activity in the moderate group compared to the mild group. In the sitting knee flexion task, only BF demonstrated a main effect ($p=0.05$) with significantly greater activation in the mild group compared to the moderate ($p=0.037$). TA demonstrated a main effect in both the sitting dorsiflexion (DF) ($p=0.017$) and standing DF ($p=0.013$) tasks, although only the sitting DF demonstrated a significant increase in activation for the moderate group, compared to the severe ($p=0.018$). Standing knee flexion demonstrated a significant main effect among a majority of muscles: SOL ($p=0.32$), MG ($p=0.19$), VM ($p=0.013$), BF ($p=0.0.1$), SM ($p=0.011$) and GM ($p=0.002$). Of these, the BF ($p=0.008$), SM ($p=0.006$), and GM ($p=0.001$) demonstrated significantly higher activation in the mild hemiparesis group. Even though there are significant differences among muscles, there are no mass extension or mass flexion patterns noticed in the more complex tasks for the moderate and severe groups, and generally mild hemiparesis is represented by increased activation of the primary movers.

Assessing Walking EMG Patterns with FMS Severity

Among those with hemiparesis, only Phase 2 (0.026) and Phase 4 (0.011) of the RF demonstrate a main effect among the severity groups (Figure 3-4). In Phase 2, the moderate and severe groups demonstrate a decrease in activation, while these same groups demonstrate an

increase in activation in Phase 4 compared to those with mild hemiparesis (RF Phase 2 p=0.027 and RF Phase 4 p=0.044).

Observationally, large bursts are seen consistently in Phases 1 and 4, representative of paretic limb loading and swing initiation, respectively. The control curve, however, is much more differentiated and shows additional bursting in the MG and GAS consistent with late stance plantarflexor activity. Additionally, the control curves demonstrate increased late swing activity (Phase 6) in the BF and SM consistent with limb deceleration, preparation for initial contact.

Fugl-Meyer and Walking Performance

Of the six clinical and biomechanical measures of walking performance examined, walking speed, BBT, and PSR were significantly correlated with the FM-LE, while only the walking speed and PSR correlated significantly with the FMS (Taable 3-1).

Non-Negative Matrix Factorization and Walking Performance

When participants were characterized by the number of NNMF factors required to explain their EMG variability, there was strong evidence for correlation with all variables ($p<.025$) (Table 3-2).

Discussion

When examined against a battery of clinical and biomechanical walking measures, the FM-LE and FMS both correlated significantly with self-selected walking speed and PSR, and the FM-LE was additionally correlated with the BBT. The correlation with walking speed is consistent with previous reports in the literature(Nadeau et al., 1999) and likely reflects the general motor impairment that is present in this clinical population. Similarly, while establishing correlations between the FMA and both self-selected and fastest comfortable walking speeds, Nadeau et al. also performed a regression analysis using the FMA (balance, FM-LE, and sensation portions entered separately), a spasticity index, isometric dynamometry scores, and

spatiotemporal analysis values into a multiple regression model to examine specific contributions to the walking speed. Hip flexor strength, balance, and FMA were all significantly correlated to both self-selected and maximal walking speeds, but the multiple regression analysis indicated that only the hip flexor strength was predictive of self-selected walking speed. Hip flexor strength, sensation of the lower extremities, and plantarflexor strength were all predictive of maximal walking speed, but again, the FMA was not part of the predictive model.(Nadeau et al., 1999)

This failure of the FM-LE to contribute significantly to a predictor model is true for walking speed as well as functional walking profiles such as the Functional Ambulation Categories (FAC) (Kollen et al., 2005). In this study, assessments were taken longitudinally 18 times during the first year post-stroke and included the following measurements: FAC, FM-LE, Motricity index leg score, letter cancellation task (LCT), FM-balance, and the timed balance test (TBT). The primary outcome measure of the study was the change over time of the FAC and the contribution of other outcomes to the regression model. All of the covariates listed above were significantly correlated with the FAC change score when analyzed with a bivariate regression model, with TBT having the strongest relationship, followed by FM-balance, FMA, LCT, and Motricity index. Multivariate modeling indicated that when all of the above factors were combined into a single regression model, the model only predicted 18% of the change in the FAC (Kollen et al., 2005).

It is inconsistent with previous literature that Pp did not significantly correlate with hemiparetic severity, as previous reports from our laboratory found significant correlations between Pp and Brunnstrom levels (Bowden et al., 2006). However, this earlier sample had a higher level of ambulatory function (0.77 $\pm$ 0.34 m/s in the earlier sample versus 0.57 $\pm$ 0.24 m/s

in the current sample). In addition, Pp was calculated in the current manuscript using the absolute deviation from the normal value of 0.5, whereas in the previous sample, Pp was treated as a continuous variable and raw values were correlated with Brunnstrom levels and not raw Fugl-Meyer scores. Another possible cause of this difference is the calculation of paretic propulsion from treadmill walking, as some investigators have argued that TM walking differs from overground walking (Harris-Love et al., 2004). However, comparisons between treadmill walking and overground walking in healthy controls yield no significant differences in the anterior propulsive forces (Goldberg et al., 2008). Additionally, the instrumented treadmill used in this experiment was recently demonstrated to be valid for laboratory gait analysis in that ground reactions, hip, knee, and ankle sagittal rotations, torques, power, and surface EMG from four thigh and leg muscles were all not significantly different than overground walking with the exception of an 8% decrease in stride length (Tesio and Rota, 2008).

When examining muscle activation patterns within the FM-LE, the clinical examination failed to distinguish hemiparetic severity consistently based on muscle activation patterns. Only supine extension and standing knee flexion demonstrated significant main effects in more than one muscle, and both showed group differences only in the BF, SM, and GM. Other than in these two tasks, EMG activity within the FM-LE is fairly consistent, regardless of severity group. Therefore, it may be inferred that four of the six tasks within the FM-LE offer practically no information regarding hemiparetic severity, at least as it relates to muscle activation patterns. The supine extension task illustrates the interesting finding of increased BF, SM and GM activity in the most mildly hemiparetic group, indicating that these muscle groups may be active as hip extensors during the task. A limitation of the FM-LE is that there are no other extension tasks to which the supine extension results may be compared. Conversely, the BF, SM and GM are

significantly more active in the standing knee flexion task in the mild hemiparesis group, indicating increased muscle activity during a flexor phase. This flexibility of response seen in the mild group may reflect adaptability within the nervous system that is not seen in those with moderate and severe hemiparesis. Alternatively, those with more severe hemiparesis may not be able to activate the BF, SM and GM during the tasks, but there is no evidence of mass extension and flexor patterns as the theory behind the FM-LE would assert. In analyses of voluntary single-plane motions while in a functionally significant standing position, Neckel et al. demonstrated that while individuals post stroke produce reduced torque in six of the eight motions in the paretic leg, they used similar strategies to controls in seven of the motions (Neckel et al., 2006). The only evidence of an abnormal synergy pattern producing the desired movement emerged with maximal hip abduction when hip flexor torque was also recorded in the stereotyped "flexor synergy" activity (Neckel et al., 2006).

EMG analysis of walking further illustrates the inability of the FM-LE to differentiate between hemiparetic severities as only the RF demonstrates any differences among the severity groups, as the mild group differs from the moderate in phases 2 and 4. This analysis also fails to illustrate any type of mass extension or flexion strategy in the severe and moderate groups. What is seen during the walking trials is a consistent burst of activity in paretic loading and paretic pre-swing. This reflects a non-differentiated burst of activity across all measured muscles when activation is required to stabilize the body or prepare for swing initiation. Although only significant in the RF, several other muscles (TA and GM) demonstrate an increased peak in Phase 4 for the severe hemiparetic group, even when activity in those muscles is not generally associated with pre-swing activity. The controls, on the other hand demonstrate additional peaks, namely during Phase 3 for the SOL and GAS and Phase 6 for the BF and SM.

These four peaks seen in the control group are consistent with NNMF analysis which indicates four factors explaining normal locomotion (Clark et al., 2008). These four factors are associated with weight acceptance (at approximately 10% of the gait cycle), propulsion (at approximately 45% of the gait cycle), ground clearance (at approximately 70% of the gait cycle), and leg deceleration during the end of swing (at approximately 95% of the gait cycle). These factors and their timing correspond very well to the peaks seen in phases 1, 3, 4, and 6. As those with hemiparesis have fewer peaks of activity, this too may reflect a decrease in the number of factors required to explain the EMG activity in walking. Seventeen individuals with stroke required only two factors, 15 required three, and only two required four factors to explain the variance in their EMG. Table 3-2 illustrates the degree to which classification by NNMF factors differentiates walking performance measures, which is more highly effective than by FM-LE or FMS (Table 3-1). These data strongly imply that an increase in NNMF factors is associated with increased complexity of the motor pattern and differentiation of muscle activation. Perhaps because NNMF is based on data collected while a participant is walking, its construct may more closely reflect walking performance than an assessment whose construct is based on voluntary, isolated movements as in the FM-LE.

Inter-subject differences in the complexity of the walking pattern revealed by NNMF may reflect the differences in the interaction of supraspinal, spinal, and peripheral input following stroke. Current evidence does not suggest either that human walking is controlled exclusively by the spinal cord or that the motor cortex alone is responsible for activation of muscles during walking (Nielsen, 2003). Emergence of an increased number of factors explaining EMG variability and the relationship of those factors with clinical and biomechanical measures of performance may reflect the integrity of descending motor pathways. However, this emergence

of complexity of behavior may also relate to activity in the periphery such as integration of spinal neuronal circuitry and processing of afferent signals. While additional work is necessary to delineate the role and neural mechanisms of spinal modules of motor control, it may be that these modules are integral to the coordination of multiple inputs for the control of human locomotion.

At this time, the number of modules as determined by NNMF is not appropriate to serve as a clinical measure because of the need for EMG data and detailed mathematical analyses. However, the FM-LE appears to be insufficient to capture necessary information about walking performance, and its use as an outcome measure for post-stroke motor control should be limited to non-walking related activities. The FMA's effectiveness as a measure of upper extremity motor control may be related to the more direct corticospinal connections to the arms and decreased reliance on patterned, spinally-modulated movement (Nakayama et al., 1994; Sanford et al., 1993). Future work developing clinical analogs to assess and monitor presence and/or emergence of NNMF factors may greatly assist clinicians in accurately describing walking-specific motor control post-stroke.

Table 3-1. Fugl-Meyer and walking performance measures

	SPEED	BBT	DGI	Pp Deviation	PSR Deviation	PPS
FM-total LE	**r=0.588** **p<0.001**	**r=0.369** **p=0.032**	r=0.116 p=0.534	r=-0.075 p= 0.674	**r=-0.357** **p= 0.038**	r=-0.291 p= 0.126
FM-Synergy	**r= 0.456** **p=0.007**	r=0.325 p=0.061	r=0.058 p=0.758	r=-0.149 p= 0.400	**r=-0.365** **p= 0.034**	r=-0.258 p= 0.177

Table 3-2. NNMF correlations with walking assessment measures

	SPEED	BBT	DGI	Pp Deviation	PSR Deviation	PPS
NNMF Factors	**r= 0.451** **p=0.008**	**r= 0.504** **p=0.003**	**r= 0.545** **p=0.002**	**r=-0.389** **p= 0.023**	**r=-0.558** **p= 0.001**	**r=-0.398** **p= 0.020**

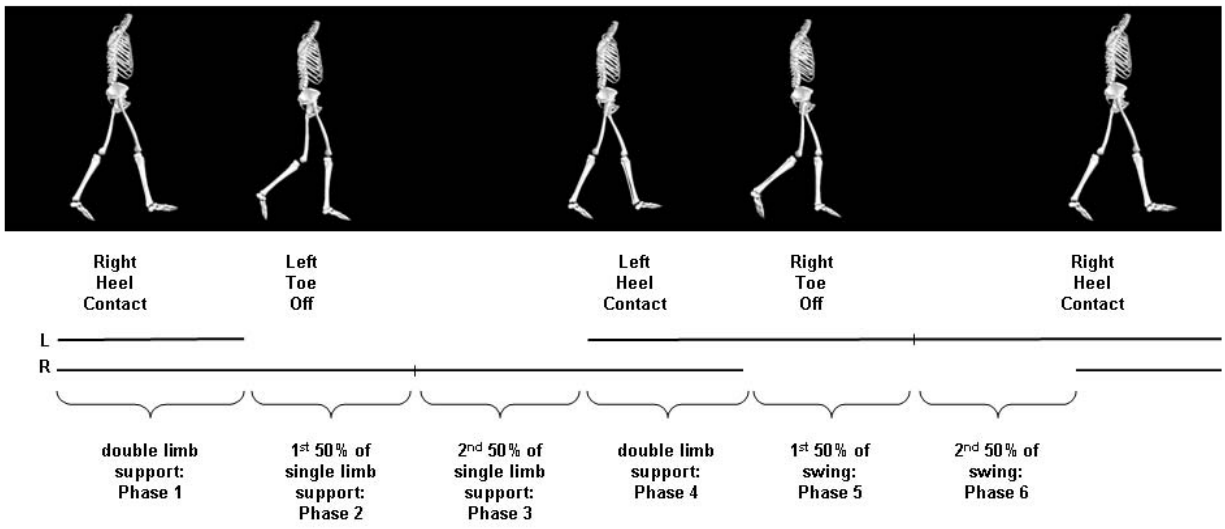

Figure 3-1. Phase descriptions for the gait cycle for someone with right hemiparesis. The first double support phase defines Phase 1. Phases 2 and 3 are the first and second 50% of the single limb support. The second double limb support (paretic pre-swing) is defined as Phase 4. Phases 5 and 6 are the first and second 50% of the swing phase.

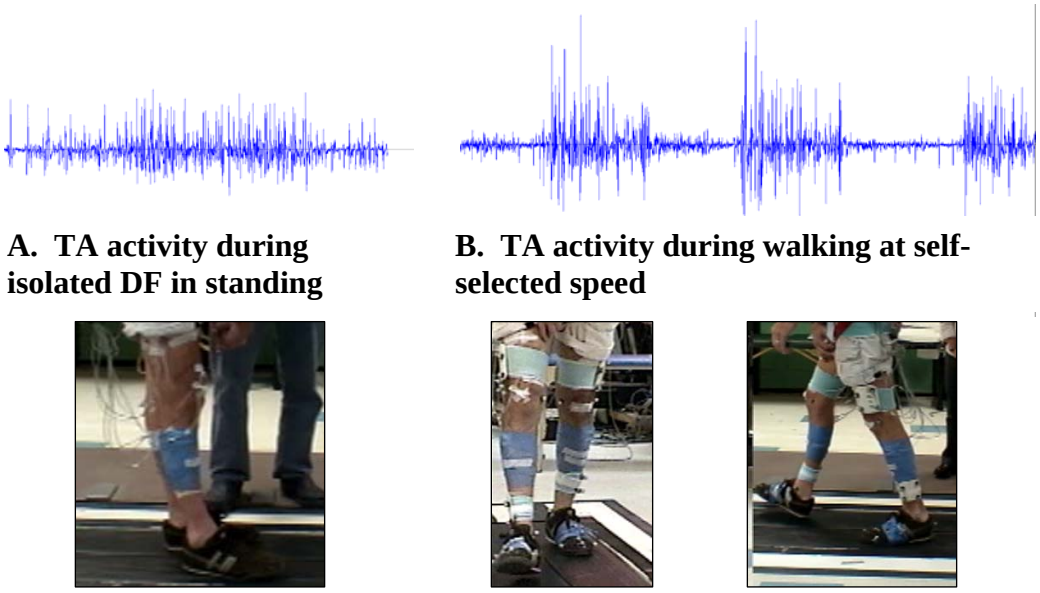

Figure 3-2. Tibialis anterior (TA) bursting patterns during right isolated DF (A) and during walking (B). Axes are identical for the two tracings. Notice the higher amplitude and clear bursting pattern in walking (B) compared to the fairly tonic activity in isolated movements (a). In addition, notice the lack of DF movement in (a) compared to functional right DF during the walking cycle in (b).

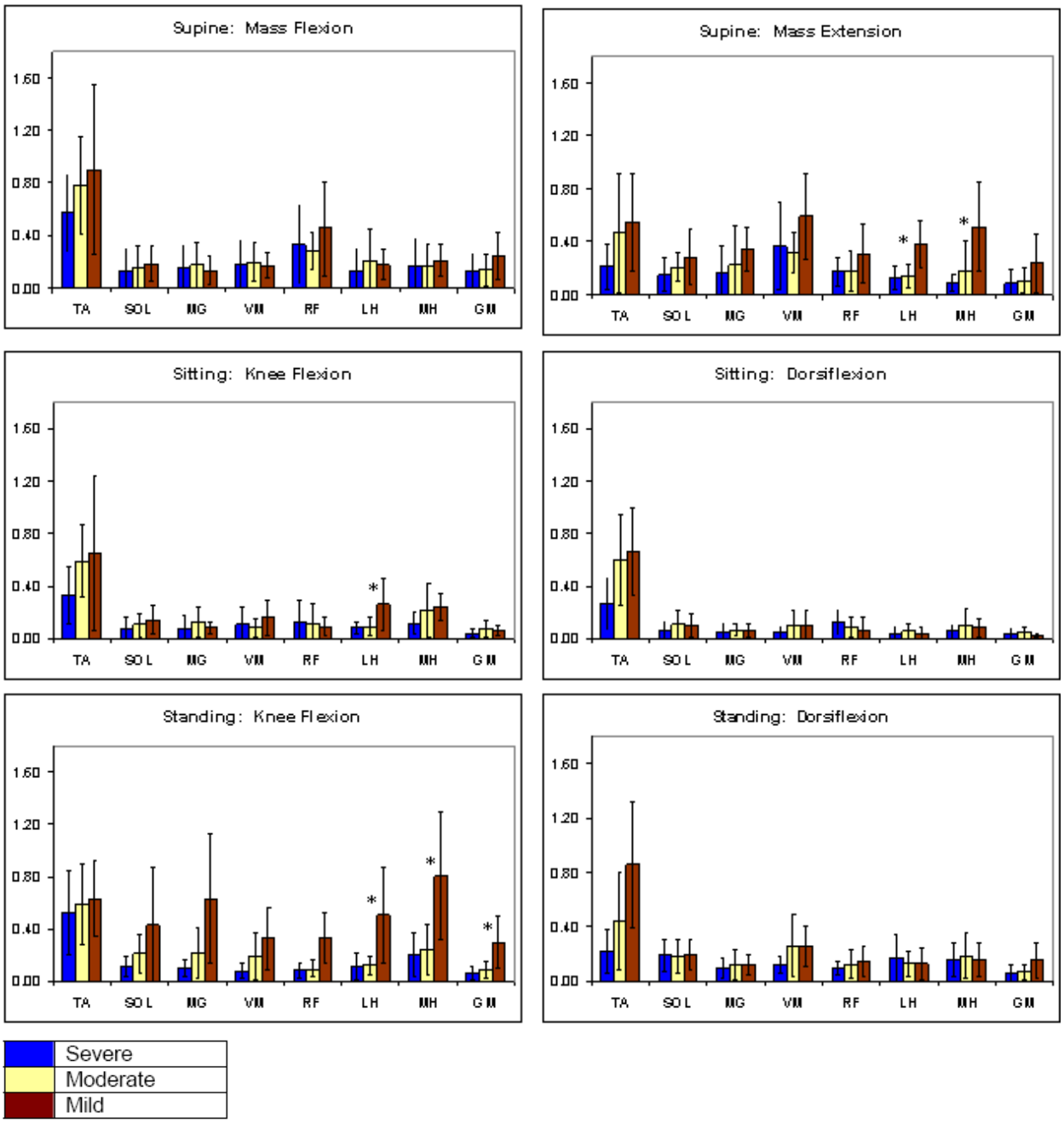

Figure 3-3. FM-LE and EMG activation. Bars reflect standard deviations. Significant differences between FM-S groups are only noted for TA in the sitting dorsiflexion task and for BF, SM, and GM in supine extension and standing knee flexion. Additionally, BF is significantly different in sitting knee flexion. However, there are no mass extension or mass flexion patterns noticed in the more complex tasks for the moderate and severe groups and generally mild hemiparesis is represented by increased activation of the primary movers. (*denotes significant differences)

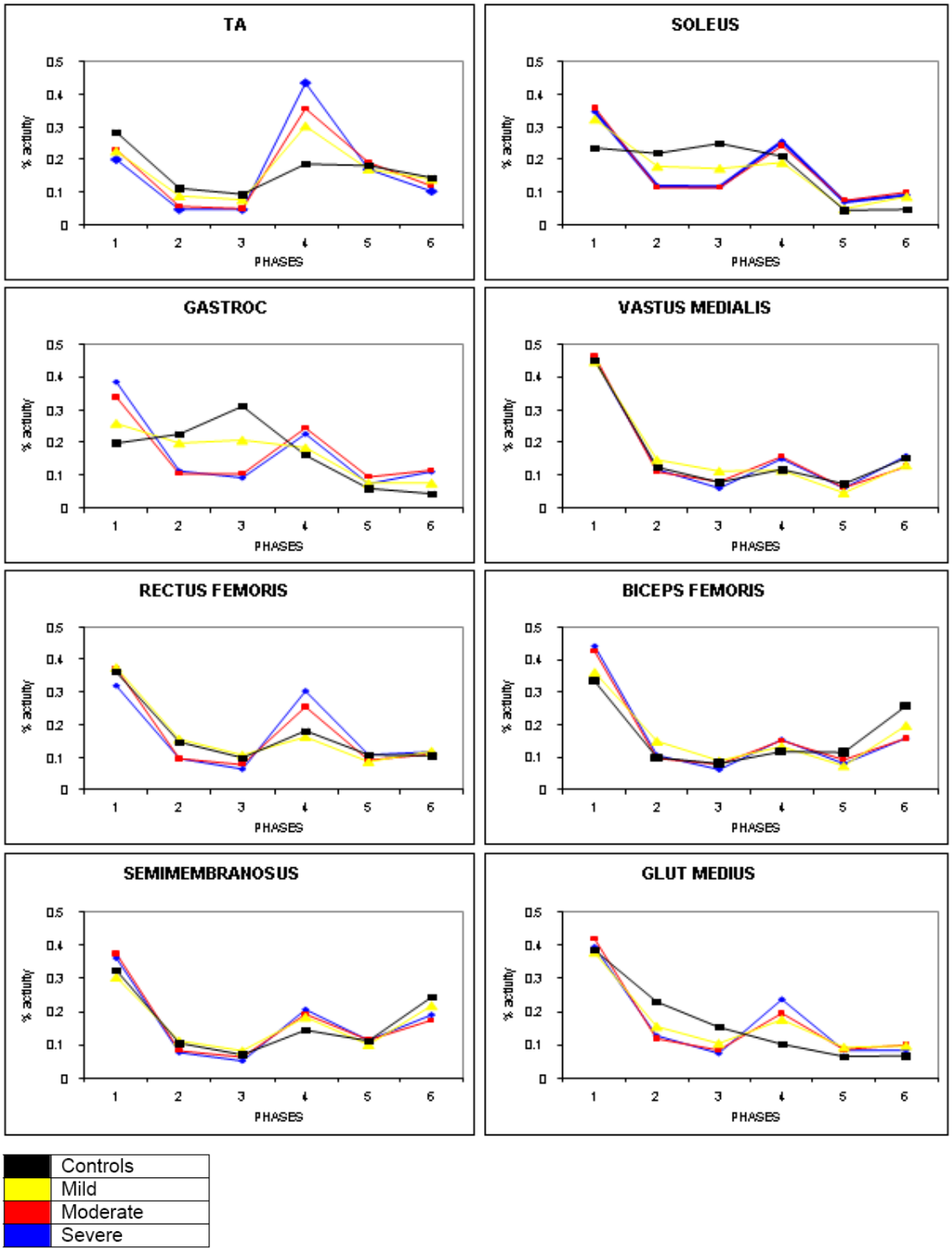

Figure 3-4. Walking EMG patterns with FMS severity. Significant differences between FM-S groups are only noted for RF for Phases 2 and 4, demonstrating that those in differing FM-S generally activate similarly during walking. Differences from control subjects (black line) can be clearly noticed in TA, SOL, GAS, and GM. (*denotes significant differences)

CHAPTER 4
MODULATION OF CUTANEOUS REFLEXES POST-STROKE: RELATIONSHIP TO WALKING PERFORMANCE AND INTERLIMB COORDINATION

Introduction

Human walking is thought to be a combination of supraspinal input, peripheral sensory signals, and activity from a complex system of spinal interneurons, often referred to as a central pattern generator (CPG) (Nielsen, 2003; Zehr, 2005). Dating back to Sherrington's groundbreaking work in the early part of the 20th Century (Sherrington, 1906), the role of sensory inputs in eliciting reflex responses has provided a mechanism by which researchers can assay the central nervous system, and considerable recent work has focused on the Hoffmann reflex (H reflex, for review see Zehr 2002 and Wolpaw 2007) (Wolpaw, 2007; Zehr, 2002) and the cutaneous afferent reflex pathways (Zehr, 2006; Zehr and Stein, 1999). The H-reflex is a very effective tool in exploring spinal cord excitability due to its mostly monosynaptic nature and ability to describe the 1a pre-synaptic reflex regulation. H-reflex amplitude, however, is modulated by both afferent feedback and central motor output. In contrast, the cutaneous reflex is not modulated by 1a afferent feedback and occurs only as a result of central motor output and specific locomotor related activity (Duysens et al., 1992; Rossi et al., 1996). Background EMG can be subtracted to yield a predominant residual reflex response (Zehr and Stein, 1999). Additionally, examination of cutaneous reflexes allows the potential to analyze different latencies of responses, reflecting polysynaptic communications among differing levels of the spinal cord and potential supraspinal circuitry (Nielsen et al., 1997).

The amplitude regulation of cutaneous reflexes is very responsive to the present functional and behavioral state of the body. These reflexes are task dependent (e.g. standing versus walking tasks) (Duysens et al., 1993), have contralateral as well as ipsilateral effects (Haridas and Zehr, 2003; Tax et al., 1995), and are phase dependent (eg. swing versus stance) (Duysens et

al., 1992; Duysens et al., 1990; Yang and Stein, 1990). The phase dependency of the gait cycle also is accompanied by reflex reversals in which the same cutaneous input evokes both facilitatory and inhibitory responses in the same muscle at differing phases of the gait cycle (Duysens et al., 1992; Yang and Stein, 1990). For example, the tibialis anterior (TA) demonstrates a middle latency (80-120 ms) excitatory response when stimulated in early swing and an inhibitory response in the swing to stance transition (Duysens et al., 1992) (see Duysens and Tax 1995 for review) (Duysens et al., 1995). Based on post stimulus time histograms of individual motor units, these reflex reversals are likely due to competing parallel facilitative and inhibitory pathways to the motor neuron (De Serres et al., 1995). This reflex reversal is most often seen in those muscles which have two periods of bursting during the course of the gait cycle (Stein, 1991). Furthermore, cutaneous reflexes appear to have a functional significance of a stumbling corrective response, which has been documented in cats (Drew and Rossignol, 1987; Forssberg, 1979) as well as humans (Zehr et al., 1997). Lastly, the neuronal mechanisms controlling cutaneous reflex responses is maintained during other locomotor tasks such as incline walking and stair climbing (Lamont and Zehr, 2006) and contribute to the maintenance of stability during walking (Haridas et al., 2005).

The activity of cutaneous reflexes during walking in populations with impaired nervous systems has been less thoroughly studied, although the reflexes are shown to be affected by central nervous system lesion. The first such study examined the cutaneous reflex behavior during walking with spinal cord injury, and found that reflexes were modulated, although exaggerated excitation predominated (Jones and Yang, 1994). Specifically, the TA demonstrated excitation throughout the gait cycle, while soleus demonstrated inhibition in stance and abnormal excitation responses during swing (Jones and Yang, 1994). Zehr demonstrated phase dependent

reflex regulation in those post stroke, indicating at least some maintenance of spinal cord level processing similar to what was seen in the control participants (Zehr et al., 1998). However, the specific pattern of regulation differed in those post stroke in that TA was strongly suppressed through early swing, soleus and vastus lateralis were suppressed throughout stance, and biceps femoris was excited only during early parts of the swing phase (Zehr et al., 1998). Interestingly, the reflex responses in stroke failed to achieve the same kinematic significance as the reflex responses in healthy controls (Zehr et al., 1998). More recently, Duysens et al. demonstrated decreased reflex activity in those with hereditary spastic paraparesis, suggesting cortico-spinal involvement in the regulation of middle latency reflexes (Duysens et al., 2004). In upper extremity assessments of individuals with acute stroke, middle and late latency reflexes were suppressed in all of the patients studied and latencies were exaggerated in the majority of individuals with sensory impairments (Chen et al., 1998). With follow-up testing over a two year period, all of the patients increased the peak to peak amplitude between excitatory and inhibitory responses (reflex modulation), although abnormalities were still apparent in two patients with motorically complete recovery. Nadler et al. found opposite results in a two year longitudinal study, demonstrating that reflex amplitude did not change over time, and found exaggerated reflexes in those that demonstrated the least motoric recovery (Nadler et al., 2004). To date, the relationship between lower extremity cutaneous reflexes and functional and/or motoric recovery has not been investigated.

Furthermore, examination of interlimb responses in those with post-stroke hemiparesis may provide insight into the functionality of interneuronal circuitry. In studying the interlimb cutaneous reflexes of the contralateral limb during walking in healthy controls, Haridas and Zehr demonstrated phase dependent regulation and reflex reversals that were significantly correlated

with kinematic changes when stimulating the superficial peroneal nerve (Haridas and Zehr, 2003). Interlimb coordination as measured with other means, however, is impaired in those with stroke. Movement amplitudes and cycle speed are decreased in tasks involving all four limbs compared to unilateral tasks in individuals post-stroke, and no facilitation of the impaired limb was found in bilateral tasks (Garry et al., 2005). In addition, Kautz and Patten illustrated that individuals post-stroke performing a leg pedaling task increased paretic leg EMG deficits when the non-paretic leg was activated (Kautz and Patten, 2005). The suppression of interlimb influences seen in controls and those post-stroke during static and discrete tasks was not demonstrated in the rhythmical leg cycling tasks post-stroke. The use of cutaneous nerve stimulation may further elucidate the impact of stroke on interlimb coordination and provide information regarding central reorganization and plasticity associated with activity-dependent locomotor retraining.

The purposes of this study are to: 1) examine the relationship between cutaneous reflex modulation and measures of behavioral recovery and functional performance in individuals post-stroke; and 2) investigate post-stroke interlimb reflex responses by examining cutaneous reflex modulation in both legs when stimuli are applied separately to the non-paretic leg and paretic leg. We hypothesized that individuals post-stroke will demonstrate decreased modulation of cutaneous reflexes and that the degree of modulation will positively correlate with measures of locomotor function. In addition, we hypothesized that individuals post-stroke will demonstrate decreased modulation of cutaneous reflexes and decreased magnitude of responses in the paretic leg during stimulation of the non-paretic lower extremity than during stimulation of the paretic lower extremity.

Methods

Participants

Fourteen individuals with chronic stroke (greater than six months post-stroke) were recruited for this study at the Gainesville, FL Department of Veterans Affairs (VA) Medical Center. Participants have a history of a single unilateral stroke, are ambulatory without contact assistance, are able to follow a multiple step command, and have no other medical issues interfering with their ability to walk. All participants signed written informed consent approved by the University of Florida Institutional Review Board and Gainesville VA Subcommittee for Clinical Investigation. Each participant underwent a walking assessment of the following measures illustrating a measure of restitution of the walking pattern (paretic propulsion), compensation of the walking pattern (walking speed), and the clinical analog of paretic propulsion (paretic step ratio).

Participants included nine with left hemiparesis and ten males with a mean chronicity of 51.5 $\pm$ 46.2 months (range 13 to 163 months), a mean walking speed of 0.72m + 0.30 m/s (range 0.31 to 1.26 m/s), and a mean stance phase of 68.51 + 4.74% of the gait cycle (range 60.3 to 76.5) (Table 4-1).

Walking Assessment Measures

Paretic propulsion (Pp). Pp is a quantitative measure of the coordinated output of the paretic leg, describing the contribution of the paretic leg in propelling the center of mass forward during walking; it is defined as the percentage of propulsion performed by the paretic leg (Bowden et al., 2006). As Pp illustrates that many of those with normal or near normal walking speeds continue to exhibit substantial motor control deficits, Pp may be an effective tool in distinguishing functional compensation from physiological restitution. Statistics will be run on the absolute deviation from normal (0.5).

Walking speed. Self-selected walking speed overground will be measured on an instrumented walkway (GAITRite, CIR Systems, Inc, Havertown, PA). Self-selected walking speed has proven to be an important measure of stroke recovery because it is simple to measure, reflects both functional and physiological changes (Perry et al., 1995; Richards et al., 1995), remains reliable and sensitive to change even as recovery advances (Richards et al., 1995), and is a predictor of health status (Studenski et al., 2003).

Paretic step ratio (PSR). PSR is defined as the percentage of stride length performed by the paretic leg and has been demonstrated to differentiate types of walking impairment post-stroke (Balasubramanian et al., 2007). PSR demonstrates a strong negative correlation (p=-0.78) with Pp, indicating that those with high PSR generate very little propulsion (Balasubramanian et al., 2007). As such, we consider PSR to be a potential clinical analog of Pp for those without access to a biomechanics laboratory. Statistics will be run on the absolute deviation from normal, symmetrical value (0.5).

Kinematics and Kinetics

Each participant completed a 30-second trial of walking on an instrumented treadmill (Medical Development, Tecmachine Hef, Andrezieux Boutheon, France) at a self selected speed to collect ground reaction forces (GRF) and kinematic data using a modified Helen Hayes marker set. A full biomechanical analysis was generated for each participant. GRF data was acquired at 200 Hz and was filtered with a low pass fourth order Butterworth filter at 20 Hz forward and backward in time. The A-P GRF component was used for analysis of the paretic propulsion. Step cycles will be identified by initial ground contact on the force plate on the paretic leg.

Electromyography

To collect electromyographic (EMG) data, the skin was shaved, abraded and cleaned with alcohol before attaching bipolar Ag-AgCl surface electrodes (Neurolog, Digitimer Ltd., Hertfordshire, England). EMG recordings were collected from four different muscles bilaterally: tibialis anterior (TA); soleus (SOL); rectus femoris (RF); and biceps femoris (BF). Data were collected at 1000 Hz and filtered with a 10 Hz high pass filter and 500 Hz low pass filter. Gains were variable from 1000 to 20,000 Hz depending on individual muscle signals. Reference electrodes will be placed over the electrically neutral patella of each leg.

Nerve Stimulation

Bilateral superficial peroneal (SP) nerves were stimulated independently on the paretic and non-paretic anterior foot/ankle using a bipolar configuration of flexible disposable 1cm Ag/AgCl electrodes (Vermed, Inc., Bellows Falls, VT). Stimulations were provided in trains of five x 1.0 ms pulses at 300 Hz using an isolated constant current stimulation (Grass S88 stimulator with Grass SIU5 and CCU1 isolation and constant current units). The intensity of the stimulation was 2.0-2.5 times the radiating threshold of each foot, not to exceed the level of noxious stimulation (Zehr et al., 1997). Stimulation should create a non-painful stimulus radiating on the dorsum of the foot into the distal second and third phalanx to assure cutaneous reflex responses and not pure flexor withdrawal responses that would be seen with a painful response. On-line assessments will be conducted to assure achievement of a reflex response during sitting with a sub-maximal isometric contraction of the TA on the stimulated leg using customized Matlab programming (the Mathworks, Natick, MA).

Each participant walked at their self-selected speed on a treadmill while applying stimulations to the SP nerve at a randomized frequency ranging from three to five seconds to assure that stimulations will not occur during consecutive steps. Each individual walked until

100 stimulations were applied, allowing for rest breaks as necessary if individuals were not capable of completing 100 stimulations consecutively. Data collection resulted in approximately 10-15 minutes of total walking.

Data Processing

EMG data was collected at 1000 Hz with a 12-bit A/D converter (National Instruments, BNC 2090) connected to a PC running customized LabVIEW virtual instruments (National Instruments, Austin, TX). Offline analysis using customized Matlab programming (the Mathworks, Natick, MA) averaged all of the step trials, dividing them into four equal proportions of the step cycle beginning with foot strike of the paretic leg. Each phase of the cycle included approximately 20-25 sweeps during which the stimulus was applied. Data were collected for each stimulation from 100 ms pre-stimulus to 200 ms post stimulus. The raw EMG signals will be rectified and filtered with a low-pass 3rd order Butterworth filter.

For each phase of the gait cycle, EMG signals from the non-stimulated sweeps will be subtracted from the average of the sweeps containing stimulations to yield the subtracted reflex trace, from which net reflex response were calculated. A significant reflex response was defined as exceeding two standard deviations above or below the non-stimulated EMG. Analyses were conducted on the middle (~75-125 ms) latency responses for the following variables: 1) peak amplitude normalized to the peak subtracted EMG for the middle latency period will be used for subsequent analyses; and 2) reflex modulation for each muscle was defined as the difference between a significant positive and negative reflex.

Baseline EMG signals were compared to EMG obtained post-stimulation and the Average Cumulative Reflex EMG after 150 ms ($ACRE_{150}$) was calculated to determine the net EMG reflex effects of the stimulation. For this measure, the EMG value at 150 ms post stimulation is divided by the time interval of integration in order to quantify a summary reflex response (Zehr

et al., 1998). The $ACRE_{150}$ was normalized to the peak undisturbed (non-stimulated) EMG signal at 150 ms post stimulation for each muscle.

Detailed descriptions of phase averaging and subtracting baseline EMG signals have been presented elsewhere in the literature (Haridas and Zehr, 2003).

Statistical Analysis

Correlations between walking performance measures and 1) reflex modulation; and 2) ACRE150 were completed using Pearson's Correlation Coefficient. Comparison of reflex responses between stimulation of the paretic and non-paretic legs were completed using a paired-sample t-test.

Results

Reflex Responses and Walking Performance Measures

When comparing the magnitude of reflex modulation in the paretic leg with measures of walking performance, Pp deviation only significantly correlated with SOL modulation when the non-paretic leg was stimulated (r=-0.581, r=0.037, Table 4-2). Self-selected walking speed was significantly correlated with TA modulation when the non-paretic leg was stimulated (r=-0.709, p=0.007, Table 4-2). PSR was not significantly correlated with the reflex modulation of any muscle, and none of the reflex modulations resulting from stimulation of the paretic leg significantly correlated with any of the walking measures. There were no significant correlations between the $ACRE_{150}$ and any of the walking performance measures.

The association between Pp deviation and the SOL modulation is consistent with the hypothesis that high degrees of walking impairment (large Pp deviation values) would be associated with smaller (shallow) modulation (Figure 4-1). The relationship between walking speed and TA modulation, however, represents a strong correlation in the direction opposite of

that hypothesized, with those walking most quickly demonstrating the shallowest modulation (Figure 4-2).

Phase Dependent Reflex Modulation

When responses from all subjects were averaged together, the paretic TA showed strong inhibitory responses, regardless of which leg was stimulated (Figure 4-3). In contrast, the paretic SOL demonstrated inhibition with paretic leg stimulation and excitation with non-paretic leg stimulation, and both of these responses were stronger in bins 1 and 2 (stance phase of the gait cycle) than in bins 3 and 4. RF and BF demonstrated more variable responses, with peak reflex activity occurring in bins 1 and 4 for the RF. In the TA, the $ACRE_{150}$ was positive for all four bins when stimulating the non-paretic leg and negative for paretic leg stimulating (Figure 4-3). Similar responses were seen in the SOL, with peaks occurring during stance (bins 1 and 2), while peaks for the TA occurred during the stance to swing transition (bin 3). Differences between stimulating sides were less evident for both the RF and BF.

In order to further examine the contributors to the reflex modulation discussed above, each of the four bins for each muscle and each participant was examined for stimulation of the paretic leg (Table 4-3) and the non-paretic leg (Table 4-4). There was a high degree of variability with the stimulation of each leg, with very few consistent patterns emerging. When stimulating the paretic leg, TA bins 3 and 4 as well as SOL bins 1 and 2 were predominantly inhibitory (highlighted red). Conversely, when stimulating the non-paretic leg, SOL bins 1 and 2 are predominately excitatory (highlighted red). These patterns were defined as having at least half the participants demonstrating significant reflexes in these bins with one or zero occurring in the opposite direction from the predominate pattern. In summary, the non-paretic leg stimulation produced reflex responses that were 70.59% excitatory, while the paretic leg stimulation elicited reflexes that were overall 68.07% inhibitory. Furthermore, stimulation of the paretic leg yielded

23 reflex reversals from a positive or negative significant reflex to one of the opposite sign within the same muscle, including five participants who demonstrated more than one reversal per cycle. In contrast, stimulation of the non-paretic leg elicited only 11 significant reflex reversals, with only one participant demonstrating more than one reversal in a muscle within a gait cycle.

Differences between Paretic and Non-Paretic Stimulation

When reflex responses were analyzed to compare stimulation of the paretic leg to stimulation of the non-paretic leg, all of the significant differences occurred in the TA and SOL (Table 4-5). Significant differences were noted for the TA bin 3 (P=0.025), TA modulation (0.013), SOL bin 1 (p=0.001), SOL bin 2 (p=0.001), and SOL bin 3 (p=0.009). This may be limited, however, to the variability of the reflex response as evidenced by the excessively large standard deviations relative to the mean in Table 4-5.

Discussion

The primary hypothesis of this experiment, that reflex modulation would correlate with measures of walking performance, is only marginally supported by the results. The SOL modulation resulting from non-paretic stimulation demonstrated a significant correlation with Pp deviation (r=-0.581, p=0.037) and the TA modulation resulting from non-paretic stimulation yielded a significant correlation with speed (r=-0.709, p=0.007) (Table 4-2). These relationships, however, occur in the opposite direction of each other, with SOL modulation increasing with decreased Pp deviation (closer to symmetrical or normal propulsion) and speed increasing as TA modulation decreases. While no other correlations with reflex modulation were significant (including none with paretic leg stimulation), these results should not be overstated, but the completely opposite relationship between speed and Pp deviation is intriguing. As Pp is purported to be a measure of motor coordination impairment and speed is at least partially a compensatory behavior (Bowden et al., 2006), it is notable that our physiological measure of

spinal level modulation demonstrates the more predictive pattern with a recovery based measure. As Pp and speed have been shown to correlate significantly in the past (Bowden et al., 2006) and approach significance in this sample ($r=-0.518$, $p=0.058$), these correlations may have very little to do with the mechanisms of how each measure is produced. The results of the current experiment are far from definitive and more research would need to be performed to address specifically the contribution of spinal reflex modulation to coordinative and compensatory measures of walking performance.

The minimal number of significant correlations between reflex modulation and walking performance measures was surprising and was perhaps due to the variability of the reflex responses in this sample. As evidenced in Tables 4-3 and 4-4, there is an absence of consistent significant reflex responses across patients and across bins. This randomness of response is particularly prevalent in the proximal musculature (RF and BF) with no specific pattern emerging from stimulation either to the paretic or non-paretic leg. The only patterns that emerged were from the distal musculature (TA and SOL), particularly TA3 and 4 when stimulating the paretic leg and SOL1 and 2 when stimulating either leg. In previous studies of individuals post stroke, co-activation patterns between the BF and RF are shown to be relatively invariant throughout recovery and are not responsive to gait interventions as applied in the study (Den Otter et al., 2006). As such, it may be that post stroke these muscles are less susceptible to reflex modulation due to the compensatory demands of hemiparetic walking. Conversely, the distal musculature may be more amenable to stimulation influences, although the functional relevance is not clear in the current investigation. Specifically, paretic stimulation yields inhibitory responses in the SOL during stance when the task requirements would indicate excitation would be required for improved stability of the stance phase. In addition, paretic leg

stimulation produces predominately inhibitory responses in the TA during terminal stance and swing when responses are expected to be excitatory to facilitate toe clearance. These deviations imply a strong irregularity in the activation of appropriate spinal interneuronal pools to produce the functionally suitable responses.

The difference between paretic and non-paretic leg stimulation was statistically significant for TA3, TA modulation, and SOL1-3 (Table 4-5). These differences may be due to the variation in activation of spinal level excitatory and inhibitory interneurons. Previous work examining interlimb coordination has speculated that this influence may be partially due rhythmic activity at the level of the spinal cord (Ferris et al., 2004; Kawashima et al., 2005). Additionally, Kautz and Patten speculated that the corticoreticular-reticulospinal-spinal interneuronal system may play a major role in bilateral coordination and specifically that the non-paretic leg can contribute greatly to the control of the paretic locomotor pattern via these interneuronal mechanisms (Kautz and Patten, 2005). Alternatively, mechanical positioning of the stimulated limb may also provide a substantial sensory input into the activation of interlimb coordination effects. In the present study, stimulation of the paretic and non-paretic legs occurred anti-phase to each other as the recorded output was always dependent on the position of the paretic leg. This mechanical influence cannot account for the lack of consistent reflex responses observed in the proximal musculature but may account for some of the phase specific differences seen in TA and SOL.

Variability within ambulation patterns post-stroke likely contribute greatly to the variability in response observed in this study. Walking post-stroke is more variable than in healthy controls for step length, swing, pre-swing and stride times; paretic swing time variability is greater than that in the non-paretic leg; and additional interlimb differences were observed for

those with more impaired gait patterns (Balasubramanian et al., 2009). In addition, EMG patterns in healthy controls demonstrate a considerable amount of variability, particularly in the proximal musculature (Winter and Yack, 1987) and it is likely that EMG patterns post-stroke present even greater variance in responses. Furthermore, animal models have demonstrated that intersubject variability is inconsistent, demonstrating varying degrees of locomotor and cutaneous reflex variance in cat hindlimbs, representing a "functional heterogeneity" in normal walking (Loeb, 1993). The above aspects of variability likely contribute in varying degrees to the lack of consistent responses to cutaneous stimulation observed in the current study. As the sample included many with a high degree of walking impairment (as determined by speed and Pp profiles), these results reflect a significant challenge in applying cutaneous reflexes studies to a broad spectrum of the hemiparetic population.

The current study is limited by the absence of exact biomechanical positions of the non-paretic limb as the gait observations were triggered by landing of the foot on the forceplate identified with the paretic side. Additional triggers for toe off on the paretic side as well as triggers for non-paretic initial contact and toe off would be required to correctly describe all of the bilateral gait events. This methodology, however, would require twice as many gait events to get an adequate number of stimulations in each bin. As such, the respondent burden may have been excessive for many of the participants in the present study as the gait performance abilities ranged from fully independent to household ambulators as defined by Perry's speed classification standards (Perry et al., 1995b). Additionally, variability of the reflex responses required collapse into four bins containing 20-25 stimulations per bin in order to observe adequate reflex activity for data analysis. This collapse further impairs the ability to describe specific gait events, particularly in bin3 which contained a mixture of stance, pre-swing and

swing events leading to a likely averaging of excitatory and inhibitory reflex responses within a bin. This is particularly true of the present sample in which the percentage of the gait cycle encompassing stance phase ranged from 60.3% to 76.5% (subject 10, for whom toe off actually occurred in bin4). Expansion to a larger number of gait bins again would have necessitated proportionately more step cycles to assure an adequate number of stimulated steps in each bin.

In addition to increasing the number of gait event markers, understanding the relationship between cutaneous reflex responses and kinetic events may add clarity the present analysis. Full kinetic evaluations to determine ankle and hip powers throughout the gait cycle were collected but analysis was not included in the present study. Additionally, it may be helpful to relate the ability to differentiate complex motor control to the ability to modulate cutaneous reflex responses. Non-negative matrix factorization of EMG walking patterns may assist in defining the differentiation of motor activity and assist in delineating those with normalized responses from those with a greater degree of variance. Again, data have been collected for this analysis, but are not included in the present study. Lastly, therapeutic programs that target the available neuroplasticity within the central nervous system may increase the amplitude of the reflex response, increase the modulation between positive and negative significant reflexes, and increase the sensitivity of the measure by reducing the amount of variability in the responses. Current evaluations are ongoing to assess the spinal cutaneous reflexes pre and post a locomotor training intervention in order to examine the potential for using cutaneous reflex studies as a marker for neuroplastic changes in those post stroke.

Table 4-1. Subject demographics

SUBJECT	PARETIC SIDE	GENDER	CHRONICITY (months)	SPEED (m/s)	% STANCE
1	Left	Male	14	0.31	65.2
2	Right	Female	60	0.63	73.5
3	Left	Male	14	0.75	67.7
4	Left	Male	43	0.97	72.6
5	Left	Male	94	1	70.8
6	Right	Male	163	0.49	72.9
7	Right	Female	13	0.33	65.4
8	Left	Male	28	0.44	67.3
9	Right	Male	41	1.11	64.8
10	Left	Female	30	0.61	76.5
11	Left	Male	18	0.63	65.7
12	Left	Male	130	1.26	73.2
13	Left	Male	26	0.49	60.3
14	Right	Female	47	1	63.2
	9L, 5R	**10M, 4F**	**51.5**	**0.72**	**68.51**

Table 4-2. Correlations between reflex modulation and walking parameters

	Pp deviation		SPEED		PSR	
NP stim TA_mod	r=-0.004	p=0.991	r=**-0.709**	p=**0.007**	r=0.420	p=0.153
NP stim SOL_mod	r=**-0.581**	p=**0.037**	r=-0.083	p=0.788	r=-0.205	p=0.501
NP stim RF_mod	r=-0.325	p=0.279	r=0.353	p=0.236	r=-0.423	p=0.149
NP stim BF_mod	r=-0.314	p=0.297	r=0.349	p=0.242	r=-0.093	p=0.763
P stim TA_mod	r=0.340	p=0.234	r=-0.387	p=0.172	r=-0.038	p=0.897
P stim SOL_mod	r=-0.078	p=0.792	r=-0.215	p=0.460	r=-0.021	p=0.944
P stim RF_mod	r=0.291	p=0.313	r=-0.393	p=0.165	r=0.077	p=0.793
P stim BF_mod	r=0.282	p=0.328	r=-0.175	p=0.549	r=-0.166	p=0.572

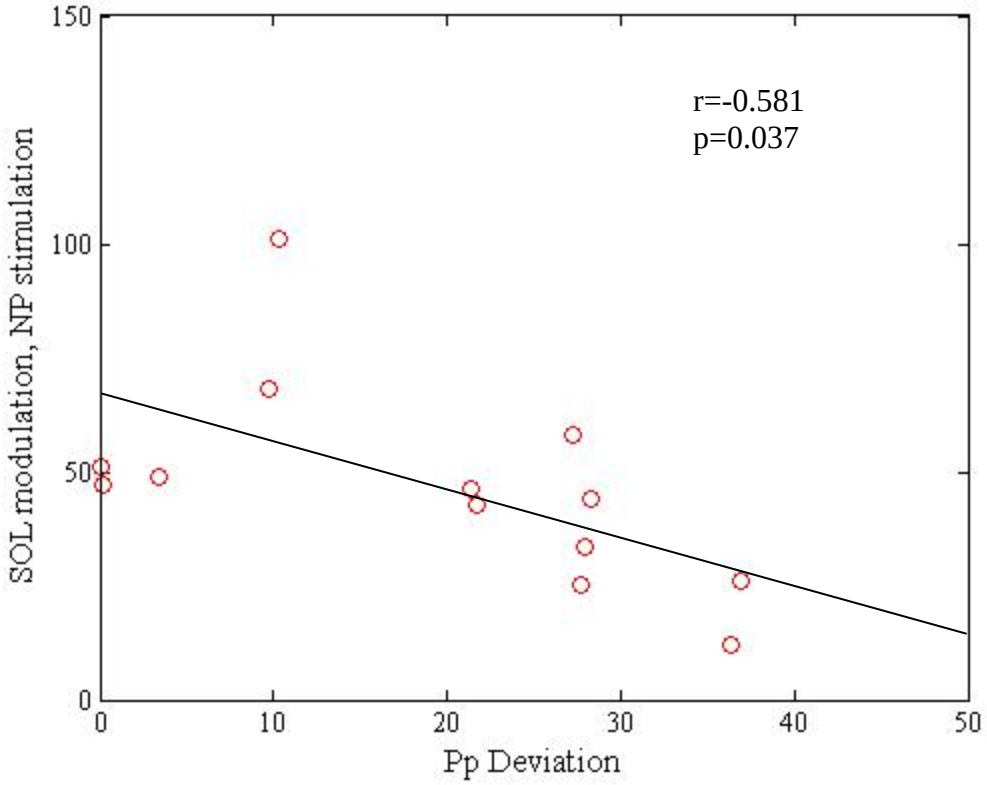

Figure 4-1. Relationship between soleus modulation and paretic propulsion deviation (stimulating the non-paretic leg). Increased modulation is significantly associated with smaller Pp deviations from symmetry.

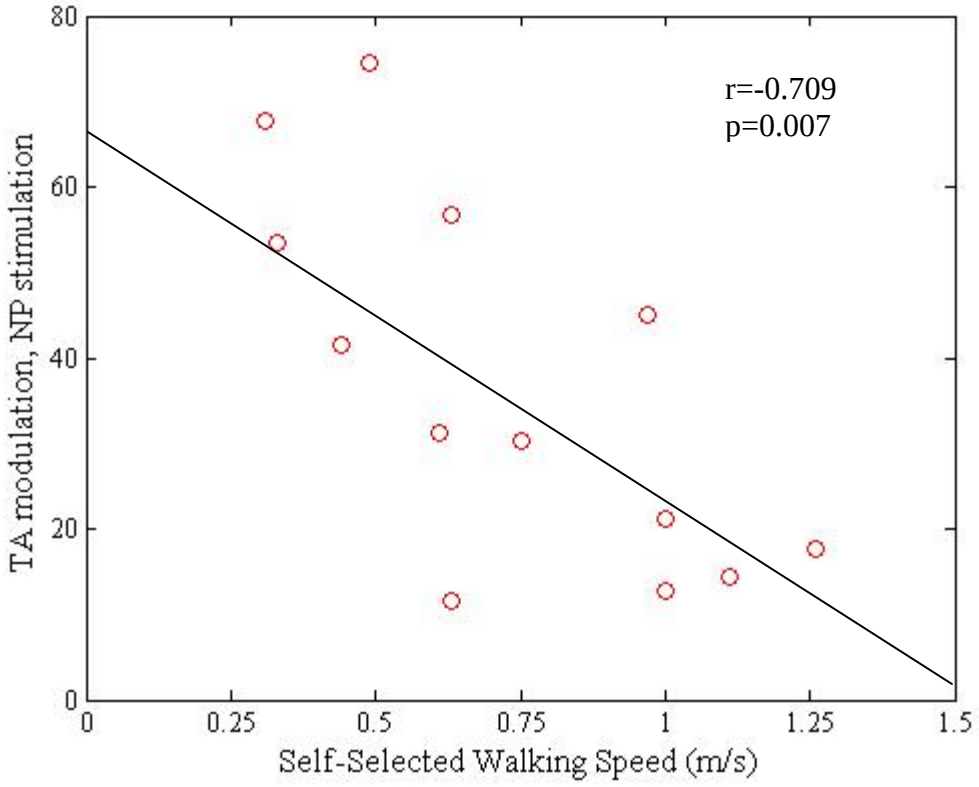

Figure 4-2. Relationship between tibialis anterior modulation and walking speed (stimulating the non-paretic leg). Increased modulation is significantly associated with faster walking speeds.

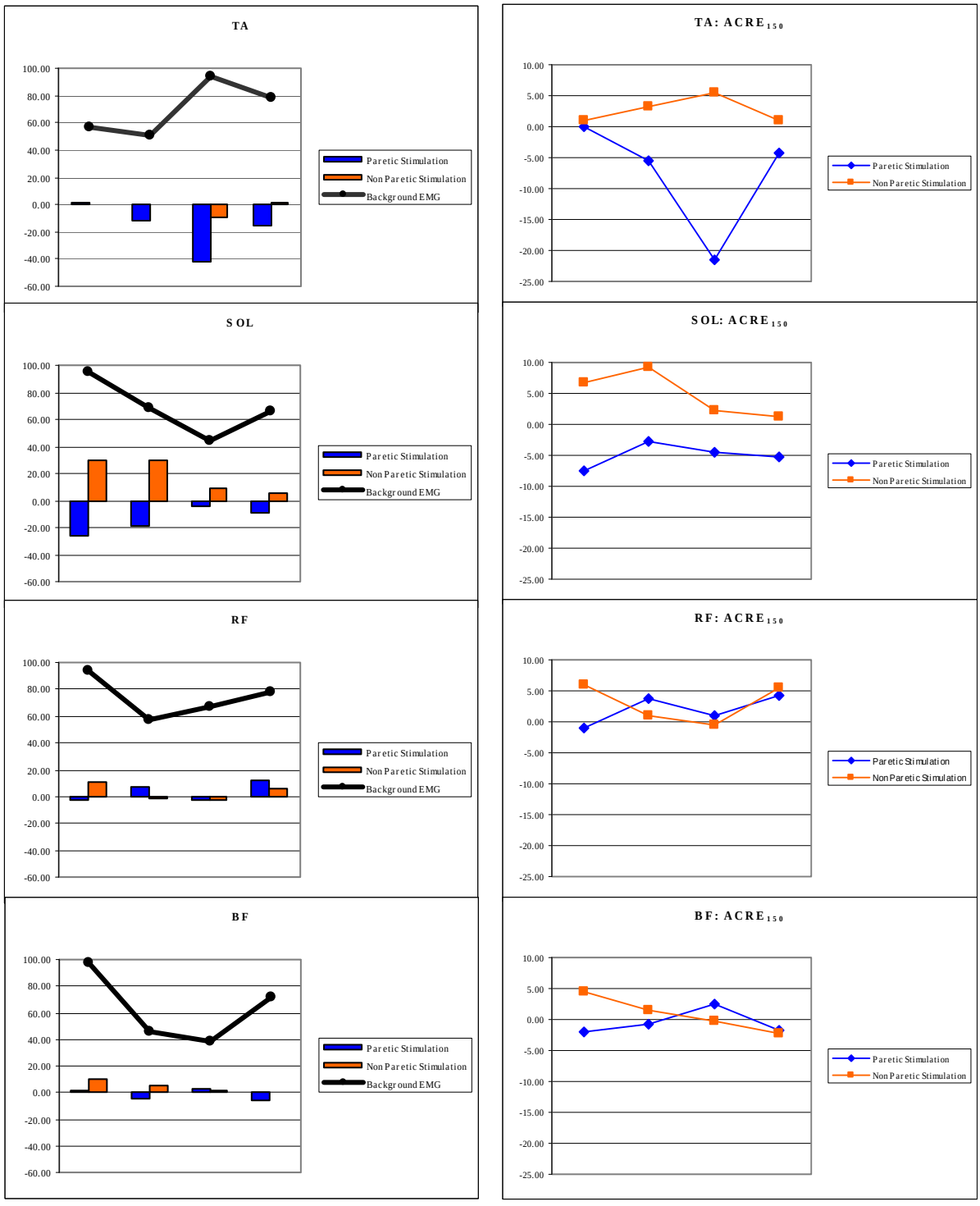

Figure 4-3. Normalized middle latency reflex and background EMG (Left Column), and $ACRE_{150}$ (Right Column) for targeted muscles. Blue bars and lines indicate stimulation of the paretic leg, while orange bars and lines indicate stimulation of the non paretic leg. Note the discrepancy in responses between stimulation sides for both the individual reflexes amplitudes and the cumulative reflex response ($ACRE_{150}$).

Table 4-3. Paretic reflex activity with paretic leg stimulation

	Tibialis Anterior				Soleus				Rectus Femoris				Biceps Femoris						
	1	**2**	**3**	**4**	**1**	**2**	**3**	4	1	2	3	4	1	2	3	4	TOTAL +	TOTAL -	Reversals
Subj1	-	-	-	-	-	-	-	-	-		+	+	+		+		4	9	1
Subj2	-	-	-	-					-	+	-		+		-	+	3	7	4
Subj3					-	+		+					+			+	4	1	1
Subj4	-	+	-					+		-	+		-		+		4	4	4
Subj5	-	-	-	-	-					-	-		+	+			2	7	0
Subj6			-		-	-	-	-		+		+		-	+		3	6	1
Subj7	+	-	-	+	-	-	+	-	+		+		+	-	-		6	7	5
Subj8	+	-	-	-		-	-	-	+	+	-	+	-		-	-	4	10	3
Subj9			-	-	-					-	-						0	5	0
Subj10			+		-	-		-	-			+	+			-	3	5	2
Subj11			-		-	-				+			-	-	+		2	5	1
Subj12				-	-	-			-			-				+	1	5	0
Subj13	-			-			-		+		-						1	4	1
Subj14			-		-	-	-					+		-		-	1	6	0
Total																	38	81	23
																	68.07% inhibitory		

Table 4-4. Paretic reflex activity with non-paretic leg stimulation

	Tibialis Anterior				Soleus				Rectus Femoris				Biceps Femoris						
	1	2	3	4	**1**	**2**	**3**	**4**	**1**	**2**	3	4	1	2	3	4	TOTAL +	TOTAL -	Reversals
Subj1			+	-	+	+		+			+	+					6	1	1
Subj2		+			+				+		+				-	+	5	1	1
Subj3						+	+			+				-	+		4	1	1
Subj4				+		+	+	+		+	+		+	+		+	9	0	0
Subj5				-	+			-	+							+	2	2	1
Subj6			-	-	+	+	+						+		-	-	4	4	1
Subj7	+	+		+	+	+	+				-				+		7	1	0
Subj8		-	+	+					+	-	-	+	-				4	4	3
Subj9			+		+				-		-					+	3	2	0
Subj10		-			+	+						+	+				4	1	0
Subj11			-	+	+	+	-				-		-			-	3	5	2
Subj12	-	-			+	+							+		+	-	4	3	1
Subj13																			
Subj14									+	+	+	+	+				5	0	0
Total																	60	25	11
																	70.59% excitatory		

Table 4-5. Comparisons between paretic and non-paretic stimulation paretic reflex activity

	Mean	Std. Deviation	t	Sig.
Tibialis Anterior bin 1	2.501	32.435	0.278	0.786
Tibialis Anterior bin 2	-11.413	23.521	-1.749	0.106
Tibialis Anterior bin 3	**-35.491**	**49.843**	**-2.567**	**0.025**
Tibialis Anterior bin 4	-15.916	30.253	-1.897	0.082
Tibialis Anterior Modulation	**30.226**	**37.549**	**2.902**	**0.013**
Soleus bin 1	**-58.415**	**45.066**	**-4.674**	**0.001**
Soleus bin 2	**-51.228**	**40.804**	**-4.527**	**0.001**
Soleus bin 3	**-12.560**	**14.482**	**-3.127**	**0.009**
Soleus bin 4	-14.850	31.367	-1.707	0.114
Soleus Modulation	-5.626	24.173	-0.839	0.418
Rectus Femoris bin 1	-15.615	45.011	-1.251	0.235
Rectus Femoris bin 2	8.505	32.785	0.935	0.368
Rectus Femoris bin 3	1.439	22.314	0.232	0.820
Rectus Femoris bin 4	7.883	25.824	1.101	0.293
Rectus Femoris Modulation	19.800	35.110	2.033	0.065
Biceps Femoris bin 1	-8.759	45.003	-0.702	0.496
Biceps Femoris bin 2	-8.343	24.006	-1.253	0.234
Biceps Femoris bin 3	0.535	20.997	0.092	0.928
Biceps Femoris bin 4	-7.926	36.281	-0.788	0.446
Biceps Femoris Modulation	5.892	31.373	0.677	0.511

CHAPTER 5
DISCUSSION

Background

Recovery post stroke has traditionally been defined by impairment level clinical scales or observations of functional behavior and has been limited by expectations associated with pre-conceived notions of the time-dependent patterns of recovery. It is unclear, however, how current clinical scales delineate restitution of pre-morbid motor behavior from compensated functional pattern of movements. Walking speed, for example, is an often used clinical measure of stroke recovery because it is simple to measure, reflects both functional and physiological changes (Perry et al., 1995b; Richards et al., 1995a), remains reliable and sensitive to change even as recovery advances (Richards et al., 1995a), and is a predictor of health status (Studenski et al., 2003). Self-selected walking speed has been associated with discrimination of potential for rehabilitation (Richards et al., 1995b), prediction of falls and fear of falling (Maki, 1997), and as functional health in the aging population (Studenski et al., 2003). However, gait speed may be increased by a variety of mechanisms, including but not limited to improved motor activation, increased peripheral strength, improved cardiovascular capacity, and improved confidence of performance. While examination of walking speed gives an indication of the functionality and independence of the task, and examination of the task underpinnings gives evidence regarding the composite mechanisms, very few measures exist to evaluate within task restitution of the behavior.

In recent years therapy has shifted from being based predominately on treatment of impairments to being based on task specific activities encouraging patients to activate their paretic limbs and not rely on compensatory techniques. This task specific, or activity based, training approach is largely driven by our current knowledge of neuroplasticity. Previous

theoretical frameworks have been dominated by the notion that the central nervous system is hard-wired and incapable of self-repair (Ramon y Cajal, 1928). However, recent technological advances in the domain of measurement have allowed scientists to discover that the nervous system has a tremendous ability to adapt both to damage and to behavioral interventions. Examples of these discoveries include the following: 1) different patterns of brain activation via functional imaging studies; 2) morphological changes in nerve synapses; 3) dendritic and axonal growth, contraction, and sprouting; 4) modulation of neurotransmitters; and 5) modulation of spinal level reflexes (Nudo, 2006). This knowledge of the nervous system's ability to adapt has led to a paradigm shift in the field of neurorehabilitation which is currently under extensive study in an attempt to take advantage of available adaptability and modulation potential (Behrman et al., 2006; Nadeau, 2002). Task specific interventions also imply a need for task specific evaluative tools, as the interventions may not be targeting impairments per se, but instead target the nervous system's potential ability to restore functional behavior to its pre-morbid state.

Currently Defined Patterns of Recovery

Currently, descriptions of recovery post stroke are limited to measurement of impairments at the body structure/function level and measurements of functional behavior at the activity and participation level of the International Classification of Functioning, Disability, and Health (ICF Model) (Figure 1-1). Recovery as currently measured increases sharply in the first six weeks after stroke and generally levels off from three to six months when measured by impairment level scales such as the Fugl-Meyer (Duncan et al., 1994; Kollen et al., 2005). In the large scale Copenhagen Stroke Study, recovery was defined as the ability to discharge home, and 64% of patients were able to discharge to the home environment, with 11% having severe deficits, 11% with moderate deficits, and 78% with mild deficits as determined by the locomotor portion of the Barthel Index (Jorgensen et al., 1995a; Jorgensen et al., 1995b; Jorgensen et al., 1995c). In this

study, functional recovery was completed within 12.5 weeks in 95% of the patients (Jorgensen et al., 1995a), which may speak strongly either to recovery or to the ceiling effect present within the Barthel Index. The best recovery was noted in 8.5 weeks in those with the mildest strokes and 20 weeks in those with the most severe. It has been hypothesized that this early functional return is strongly linked to natural neurologic restitution of peri-infarct tissue, recovery of diaschisis, and improved neurotransmission near and distal to the infarct site (Kwakkel et al., 2004). This "spontaneous neurologic recovery" has been demonstrated via regression models to account for 16-42% of the improvements in body structure function and activities in the first two to three months post stroke (Kwakkel et al., 2006).

In contrast to the ordinal clinical scales and subscales, walking speed is shown to reflect changes in functional recovery for up to 12-18 months post stroke, reflecting both increases in cadence and step length (Richards et al., 1992). Kollen later confirmed these results by showing longitudinal increases in walking speed over the course of a year, with self selected speed increasing from 0.037 m/s to 0.64 m/s (Kollen et al., 2006). Additionally, Kollen demonstrated that the Functional Ambulation Category (FAC) increased longitudinally over the course of a year, reflecting additional functionality associated with the increase in walking speed (Kollen et al., 2005). However, concurrently collected clinical scores such as the Fugl-Meyer lower extremity subscore, the Fugl-Meyer balance subscore, the Letter Cancellation Task, the Motricity Index, and the Timed Balance Test combined to account for only 18% of the variance in the FAC change, even though each demonstrated significant correlations with the FAC (Kollen et al., 2005). These results underscore two points: 1) that functional improvement may continue even as impairment level measurement plateaus; and 2) that correlation of clinical findings to functional performance cannot be interpreted as a cause for the change.

Using more detailed instrumentation, researchers demonstrated that electromyographic (EMG) measurements may be used to evaluate deficits in a patient's motor control. Using EMG output patterns, Knutsson and Richards identified three types of hemiparetic walking based on dependence on spasticity, amount of voluntary activation, and the amount of co-contraction (Knutsson and Richards, 1979). EMG patterns have been utilized in longitudinal assessments of patients and demonstrate improvement over a two year period that are related to changes in walking speed (Richards et al., 1995a). While bursting of the triceps surae (gastrocnemius and soleus) does not appear to change over time, the amplitude of tibialis anterior (TA) bursting does show longitudinal improvement. Those with faster walking speeds demonstrated improved movement profiles associated with increased EMG activity, while those with slower walking speeds maintain more constant profiles (Richards et al., 1995a). Proximal musculature such as the biceps femoris remains more invariant, although the quadriceps also improve their EMG activation patterns beginning at approximately one year post stroke (Richards et al., 1995a).

More recent explorations of longitudinal EMG changes were conducted in two studies investigating activation patterns resulting from therapeutic interventions in sub-acute populations. Ambulatory independence, walking speed, and mobility increased, but patterns of co-activation in the biceps femoris and rectus femoris remained relatively constant up to 10 weeks post stroke, creating consistent asymmetry in the swing phase of the gait pattern (Den Otter et al., 2006). As function improved in the absence of altered activation profiles, it was interpreted that EMG patterning changes are not necessary for functional gain. A more recent analysis demonstrated similar findings up to 24 weeks post-stroke, showing that surface EMG patterns did not change in spite of significant improvements in walking function (Buurke et al.,

2008). Both of these studies interpret these findings as a source of advocacy for compensatory based approaches to walking rehabilitation as improved muscle activity coordination is not associated with functional recovery. However, both studies utilized a traditional approach to walking rehabilitation, and it remains to be seen if contemporary task specific approaches targeting available central nervous system plasticity will yield similar responses.

As the end goal of muscle activation is to produce appropriately sized and timed rotational forces around the hips, knees, and ankles, kinetic analyses of hemiparetic walking are additionally important in understanding the achievement of improved function. Power profiles (Figure 5-1) were collected before and two months after a task oriented intervention and the H1 (hip extension during initial stance), H3 (hip flexion during early swing), and A2 (ankle plantarflexion during late stance and pre-swing) (Winter, 1990) all increased after therapy and the A2 and H3 bursts were significantly correlated with walking speed (Richards et al., 2004). Furthermore, the A2 peak burst improvement was responsible for 25% of the gain in walking. Examining the interlimb coordination effects demonstrated that pre-training, paretic A2 and H3 accounted for 84% of the variance in walking speed, while post-training the non-paretic H3 replaces the paretic H3 to account for 82% of the post-training variance in patients that improved from 0.40 m/s to 0.58 m/s as a result of the intervention (Richards et al., 2004). Parvataneni demonstrated a similar interlimb coordination effect, illustrating that the non-paretic H1 was equally important as the paretic H1 in accounting for gait speed changes from 0.69 m/s to 0.83 m/s as the result of an intervention (Parvataneni et al., 2007). These results demonstrate two primary findings: 1) that paretic H1, H3, and A2 and non-paretic H1 and H3 collectively account for changes in walking speed (Parvataneni et al., 2007); and 2) that conventional training programs are effective in training the non-paretic leg as well as the paretic. Activity based

therapies focusing on encouraging use of the paretic leg may demonstrate a different balance of kinetic profiles, and measures need to have the capability of assimilating the coordinative effects of power generation.

Neurobiological Control of Walking

The historical viewpoint of the body's potential to restore walking function emerged from the belief that all movements were originated and controlled within the cerebral cortex. This "top-down" approach is rooted in the functional neuroanatomy of the brain and its descending tracts. As can be seen in the model of the human motor homunculus (Figure 5-2), the portion of the motor cortex that is dedicated to the lower extremities largely lies deep in the interhemispheric fissure between the two cerebral hemispheres. The primary source of input into the corticospinal (CS) tract comes from the primary motor cortex, or Brodman's area 4 in the pre-central gyrus (Nadeau et al., 2004). Other projections to the CS tract emerge from the pre-motor cortex (Brodman's area 6) as well as the post-central gyrus, or somatosensory cortex (Brodman's areas 3, 2, and 1). In addition to the pre-motor and somatosensory cortexes, the primary motor cortex receives input from the primary sensory cortex, thalamus, putamen (basal ganglia), dorsal column nuclei, and the cerebellum (Nadeau et al., 2004). These fibers emerge from the primary motor cortex and travel through the corona radiata in the periventricualar white matter, through the internal capsule, cerebral peduncles, pons, medulla (pyramids) and to the contralateral spinal cord (Nadeau et al., 2004). From there, the CS synapses with peripheral nerves and produce the observed motor evoked potentials.

In contrast, recent advances in the field of locomotor recovery after spinal cord injury argue compellingly for a "bottom up" approach in which much of automatic walking and rhythm generation is controlled at the level of the spinal cord. Animal work over the past 30 years has proven that alternating activity occurs in antagonistic muscles even in the presence of complete

spinalization (Grillner, 1985; Rossignol, 2000). The presence of sub-cortical rhythmical control of walking gave rise to the description of central pattern generators (CPGs). CPGs are thought to be located at the level of the spinal cord and can be the controller of rhythmic patterned behavior such as walking (MacKay-Lyons, 2002) and breathing (Barlow and Estep, 2006). This spinal network can be activated by descending mesencephalic and subthalamic locomotor regions in a non-specific way and is capable of recruiting locomotor muscles in a coordinated fashion (Nielsen, 2003). In humans, it was demonstrated as early as 1997 that the lumbosacral spinal cord can coordinate cyclic activity in the lower extremities and may be driven supraspinally or peripherally (Harkema et al., 1997). This peripheral sensory signaling "provide cues that enable the human lumbosacral spinal cord to modulate efferent output in a manner that may facilitate the generation of stepping" (Harkema et al., 1997). Sensory feedback is thought to be critical in the effective functioning of the CPG (Nielsen, 2003).

While purely cortically driven activation may be true of non-patterned movements of the upper extremity and gait events that require adaptation to steady state patterns, the presence of sub-cortical rhythmical control may necessitate an understanding of the spinal cord's contribution to walking. Human locomotion, however, is much more functionally impaired by lesions to the spinal cord than is quadripedal locomotion, and lesions of the pyramidal tract may have much more devastating effect on humans than other animals (Porter and Lemon, 1993). Based on clinical trials of individuals with varying degrees of supraspinal control, those with clinically complete injuries demonstrate severely limited functional recovery (Dietz et al., 1995; Wirz et al., 2001), and it may be deduced that control of walking exists within some merger of the "top down" and "bottom up" approaches. As Nielsen stated in a recent review of the central control of muscle activity during walking, "it is the task of the whole central nervous system to

generate this muscle activity, to ensure that it is optimally coordinated, to ensure that it is adjusted to the immediate environment, and to modify it when required" (Nielsen, 2003). Nielsen concludes by saying that there is "no reason" to suggest that human walking is controlled exclusively by the spinal cord, nor is there a reason to imply that the motor cortex alone is responsible for activation of muscles during walking. Instead, this activity related to walking must rely on an integration of spinal neuronal circuitry, afferent signals and descending motor commands (Nielsen, 2003).

Relationship of Neural Control of Walking to Experiments

The purpose of the experiment described in Chapter 3 was to test whether the motor impairment measured by the Fugl Meyer is indicative of motor dysfunction during walking in adults with post-stroke hemiparesis. Observations in our laboratory have indicated that individuals may not be able to achieve active dorsiflexion during a supine, sitting, and/or standing position even though they have detectable bursting of EMG activity during the task. Approximately half of these individuals, however, are able not only to increase the magnitude of tibialis anterior (TA) bursting during the walking cycle, but also are able to achieve near normal dorsiflexion while ambulating. These findings reflect the complex control of human locomotion described above and may provide some observational evidence of the control of walking beyond a pure cortically driven phenomenon. As a result, we would infer that voluntary, discrete activities as performed in the Fugl Meyer may be inadequate to capture the complex motor behavior in walking. In contrast, walking specific measures are required to describe the effect of walking rehabilitation interventions on behavioral recovery.

One such task specific measure is paretic propulsion (Pp), described in detail in Chapter 2. As described, Pp represents a coordinated output of the paretic leg by representing the paretic leg's contribution to the overall anterior ground reaction force (propulsion). Subsequent

analyses have demonstrated that this mechanism occurs partly due to aberrant EMG activity of the paretic leg as it is associated strongly and positively with the plantarflexor activity of the triceps surae and is associated negatively with activity of the rectus femoris (Turns et al., 2007). This EMG activity demonstrates that those with less severe hemiparesis activate plantarflexors in the late stance phase and paretic pre-swing (when propulsion would ideally occur) while those with more severe hemiparesis demonstrate earlier flexor activity during terminal stance (as opposed to paretic pre-swing and swing when flexor activity should take place).

Pp may also be associated with the combinations of various power bursts associated with the walking cycle. Propulsion of the center of mass (COM) occurs through some combination of the three primary positive power bursts H1, H3, and A2 . By themselves, these power bursts may also reflect intralimb and interlimb compensations. For example, a weak A2 during double limb support may be compensated for by a stronger H1 in the contralateral lead leg, effectively pulling the COM anteriorly. Similarly, in the trail leg, a weak A2 burst may be compensated by a stronger H3, effectively to create a "pull off" instead of a "push off" in the trail leg. A pull off of the paretic leg would lead to a stronger ground reaction force during contralateral single leg stance as that would be the only force of contact at that moment. These patterns of compensation are clearly seen in kinetic analyses of walking post stroke (Olney et al., 1991). However, examination of these power bursts alone would not demonstrate the compensatory behavior and the overall contribution of the paretic leg. In fact, integration of the power curves yielding work profiles demonstrate that the paretic leg performs 40% of the work during walking regardless of hemiparetic severity (Olney et al., 1991). This is in direct contrast to previous reports of mechanical work in pedaling post stroke, where those with severe hemiparesis produce markedly

less mechanical work than healthy controls, and often achieve no positive work from the paretic leg (Kautz and Brown, 1998).

Perhaps the most intriguing concept regarding Pp and compensation emerges from the relationship with walking speed. While the correlation is significant, analyses of Pp clearly illustrate that those with normal walking speeds of greater than 0.8 m/s have a deficit of coordinated motor control of less than 25% of total propulsion. Unpublished work from our laboratory has also demonstrated that Pp is speed insensitive, and the percentage of propulsion from the paretic leg is independent of the speed at which one walks. This is in contrast to power, which may be specific to the speed at which one walks. As hip flexor moments and angular velocities both increase with walking speed, it should be assumed that powers would increase concordantly. Thus, Pp not only accounts for the intralimb and interlimb compensations present in a power analysis, it also controls for speed related increases in power.

Results from Chapter 4 illustrate that Pp, specifically the deviation from the symmetrical value of 50%, is negatively correlated with reflex modulation of the soleus muscle. The presented analysis does not allow for a direct determinant of the functional significance of this correlation, but as the soleus is one of the main contributors to the A2 power burst, it is of note that the impaired nervous system is able to provide heightened modulation in those with more coordinated motor output. Conversely, the compensatory based measure of walking speed demonstrates a negative correlation with tibialis anterior modulation, indicating that those who walk most quickly demonstrate the poorest modulation of the primary dorsiflexor of the ankle. Further exploration is required to glean the exact functional significance of these modulation effects.

The cutaneous reflex experiment does not provide any large degree of understanding as to the role of spinal level mechanisms in the control of hemiparetic walking nor does it illustrate a purely supraspinal mechanism. The results primarily highlight the degree of variability within the impaired central nervous system and the inability to consistently activate either excitatory or inhibitory spinal interneurons as required. The technique is still promising, however, for the illumination of a less random system as a result of interventions targeting available neuroplasticity of the nervous system. Such activity based therapies may increase the amplitude of the reflex response, increase the modulation between positive and negative significant reflexes, and increase the sensitivity of the measure by reducing the amount of variability in the responses.

Conclusion

Control of walking ability post stroke is a coordinated function relying on multiple elements of the central nervous system, peripheral motor and sensory systems, skeletal muscle function, cardiovascular potential, as well as personal and environmental factors contributing to self-efficacy. Previous reports of walking recovery post stroke have examined impairment level contributions to stroke recovery, with recent advances in biomechanical contributions in terms of EMG, kinematic, and kinetic profiles demonstrating mechanistic characteristics of improved walking. Even these mechanistic approaches, however, illustrate substantial intralimb and interlimb coordination effects and fail to adequately assess restitution of walking performance as opposed to functional compensation. These experiments highlighted one of the historical gold-standards of motor control in detail as it relates to walking performance and found it to be inadequate to describe walking specific restitution. We proposed a coordinative measure of walking performance that takes into account the compensatory limitations of looking at power burst separately, and that arguably provides a single measure to describe restitution of

performance specific to gait activity. The interplay between multiple neurobiological controls of walking is still poorly delineated, and further work is ongoing in the BRRC/University of Florida Human Motor Performance Laboratory and collaborating laboratories to examine how these influences might be addressed with future neurorehabilitation techniques. The recent onset of novel therapies, including those based on activity based neuroplasticity, necessitates that researchers and clinicians not rely on historical constructs to examine restitution of walking performance so that clinicians may more effectively understand intervention results and maximize the capacity of those we treat.

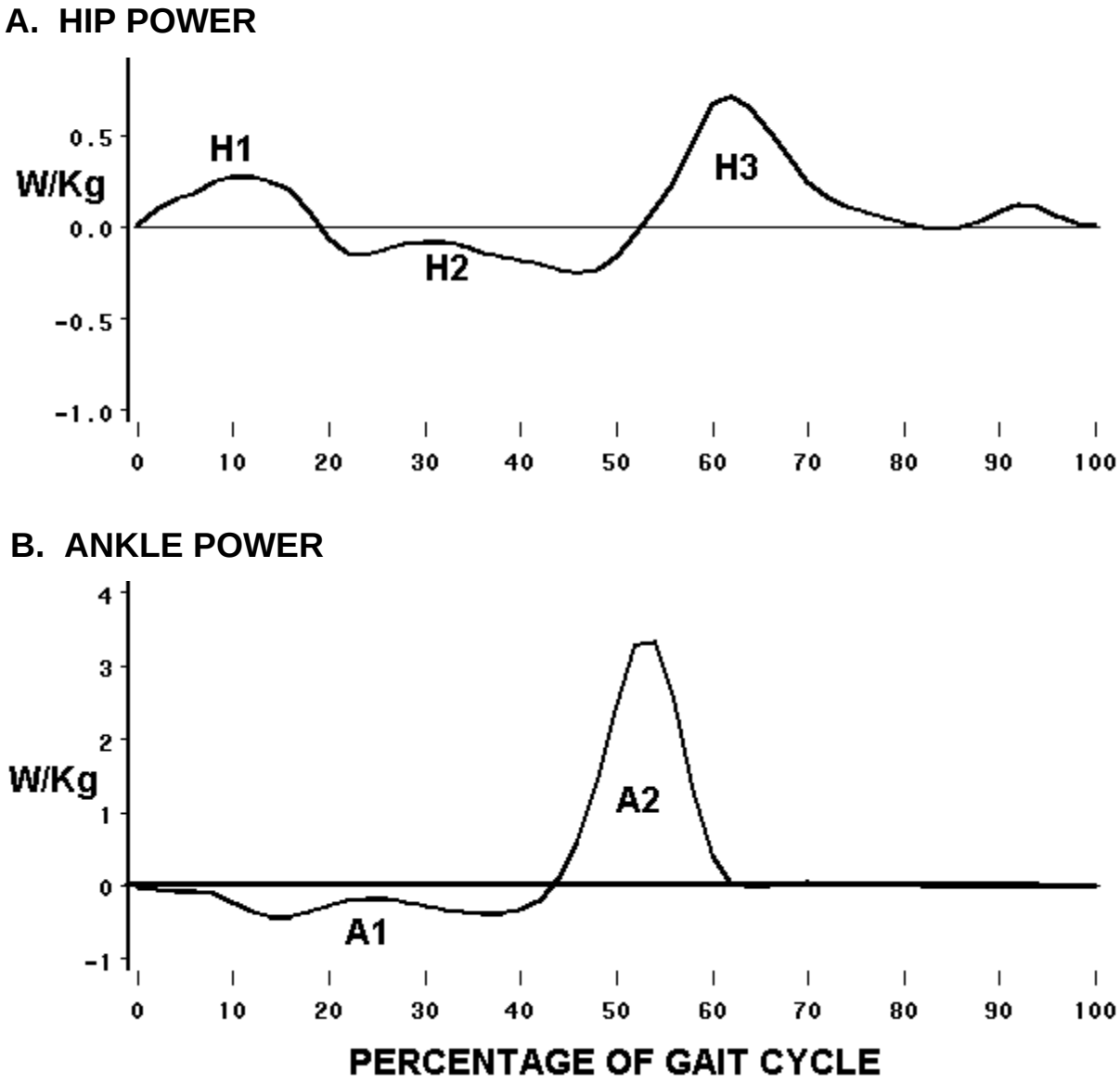

Figure 5-1. Power curves for the hip (A) and ankle (B) (From Winter DA. Biomechanics and motor control of human movement. New York, NT: John Wiley & Sons, Inc., 1990). The positive power bursts H1, H3, and A2 contribute to propulsion of the center of mass.

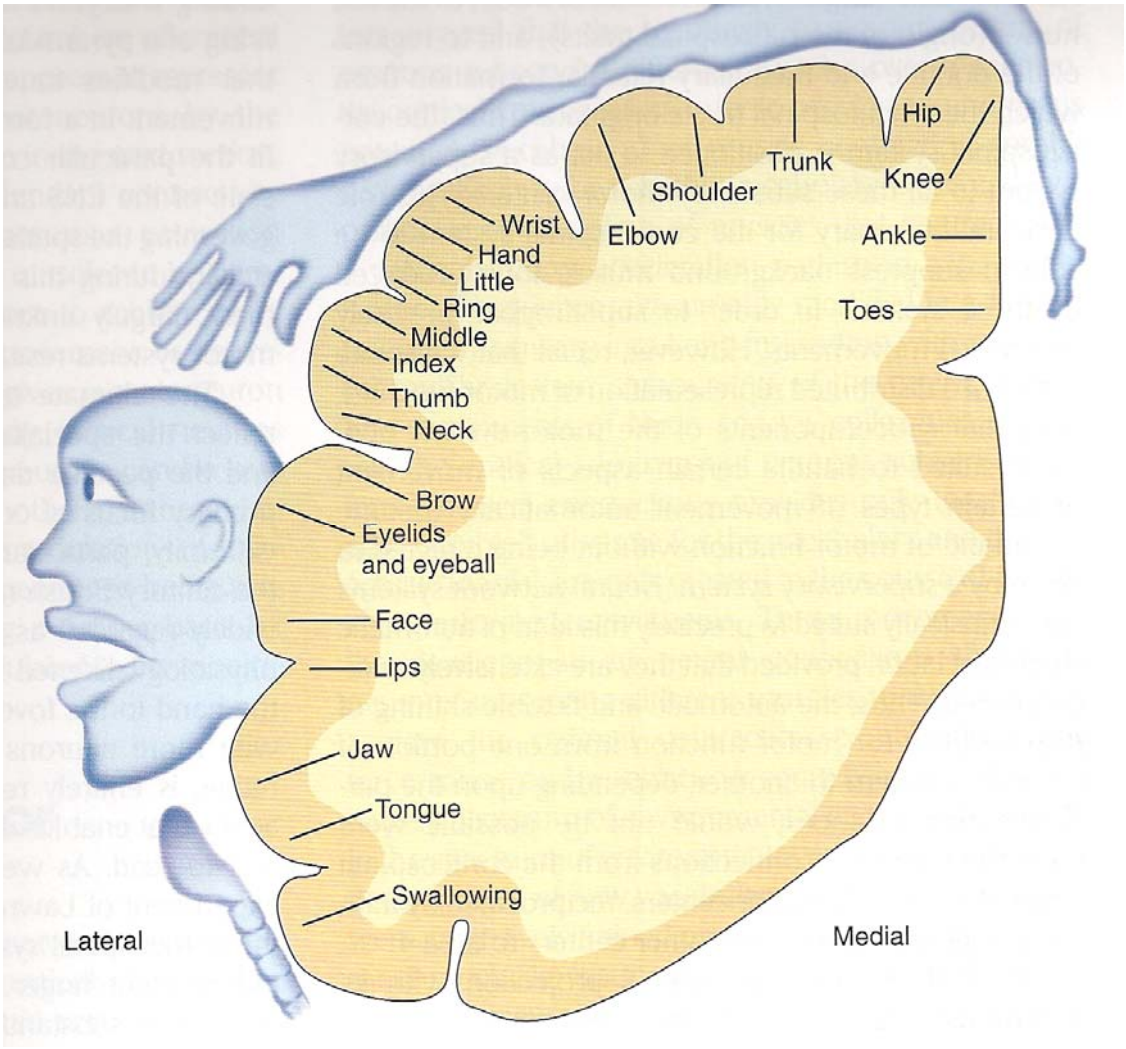

Figure 5-2. Motor homunculus (From Nadeau S, Ferguson T, Valenstein E, Vierck C, Petruska J, Streit W, et al. Medical Neuroscience. Philadelphia: Saunders, 2004). Note the minor size of the lower extremity representation and its location in the interhemispheric fissure.

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BIOGRAPHICAL SKETCH

Mark Bowden graduated from Salisbury High School in Salisbury, NC in 1987. He attended Duke University in Durham, NC from 1987 to 1991, graduating with a B.S. in psychology. After graduation, Mark worked as a research assistant in the Veterans Affairs Medical Center in Durham, NC. In 1993, Mark returned to Duke University in the master's program in physical therapy, graduating with an M.S. in 1995. Mark worked for three years as a staff physical therapist at the Charlotte Institute of Rehabilitation in Charlotte, NC, leaving in April, 1998 to become Therapy Manager of the Spinal Cord Injury Program at Methodist Rehabilitation Center in Jackson, MS. He left clinical practice in September 2002 to take the role of Research Physical Therapist at the Brain Rehabilitation Research Center in Gainesville, FL, and enrolled in the rehabilitation science doctoral program at the University of Florida in January 2004, where he graduated in May 2009 with a Ph.D. in rehabilitation science and a concentration in movement dysfunction.