ROLE OF CORTICOMOTOR DRIVE TO WALKING RECOVERY AND RESPONSES TO FUNCTIONAL ELECTRICAL STIMULATION IN STROKE SURVIVORS

Jacqueline A. Palmer

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

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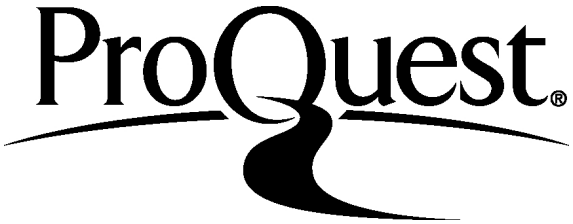

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ABSTRACT

Despite current standard rehabilitation efforts, walking deficits that contribute to limitations in activity and participation in individuals with chronic stroke persist. Recent developments in a noninvasive brain stimulation technology, transcranial magnetic stimulation (TMS), provide an opportunity to investigate neurophysiologic components underlying post-stroke motor recovery by quantifying the strength of corticomotor connectivity to specific muscles. There is evidence that the balance of corticomotor drive to paretic and nonparetic upper extremities of stroke survivors is related to motor function, can be changed through rehabilitation, and can predict functional outcomes in response to intervention. However, neurophysiologic mechanisms underlying *lower extremity* motor recovery are unknown and our understanding of rehabilitation effects on cortical factors that could influence post-stroke walking ability is poor. The overall purpose of this project was to investigate corticomotor factors underlying lower extremity clinical (aim 1) and biomechanical (aim 2) walking function following stroke. Additionally, we sought to determine the effectiveness of a single session of rehabilitation utilizing gait training with functional electrical stimulation (FES) to induce changes in corticomotor behavior that, if improved, could promote positive changes in biomechanical walking impairments (aim 3). The results of this study indicate that balance of corticomotor drive to the paretic and nonparetic lower extremities is critical to the level of walking function achieved by individuals with chronic stroke. Our results suggest that *both* the lesioned and nonlesioned motor cortices play a role in post-stroke walking recovery. This can be evidenced by the origins of corticomotor asymmetry stemming from both reduced corticomotor drive to the paretic leg *and* enhanced corticomotor drive to the

nonparetic leg in stroke survivors with poor walking recovery. These patterns of corticomotor asymmetry are different between resting and active motor states and more severely affect the ankle plantarflexor muscles than the dorsiflexor muscles. The balance of corticomotor drive between limbs affected post-stroke walking biomechanical function, as we found that corticomotor symmetry to plantarflexor muscles determined the propulsive strategy that stroke survivors used to achieve their fastest walking speeds. Critically, findings of this project further demonstrated that a single session of gait rehabilitation utilizing FES could promote corticomotor balance to plantarflexors that was positively related to improvements in biomechanical gait impairments. Together, these findings offer new insights into neurophysiologic mechanisms underlying post-stroke walking ability and identify specific cortical mechanisms that may be targeted through rehabilitation to produce positive changes in biomechanical walking function in stroke survivors.

Chapter 1

INTRODUCTION

Damage to neurophysiologic structures within the brain induced by stroke lead to a myriad of lower extremity motor impairments that affect walking ability.[1] Current standard rehabilitation efforts have enabled some individuals to regain lower extremity function, but many stroke survivors continue to suffer from long-term walking disability[2] and are unable to achieve levels of walking ability that would allow for community participation.[1] Numerous studies have shown that the central nervous system has a remarkable capacity to modify structure and function of neurons in response to environmental stimuli that can be introduced through rehabilitation.[3,4] Though it is well-established that the motor cortex is intricately and actively involved in the control of the lower extremity during human gait,[5-7] post-stroke neural recovery has not been adequately characterized in the lower extremity, creating barriers for current rehabilitation. Biomechanical investigations have identified a number of kinetic and kinematic walking impairments that influence speed and efficiency of functional ambulation,[8] and, when improved through rehabilitation, can enhance post-stroke walking function.[9] However, the neural manifestations of such post-stroke gait impairments are poorly understood, possibly attributing to the heterogeneous responses to specific rehabilitation strategies that have been consistently observed in stroke survivors.[9-11] Our long-term goals are to understand the salient neurophysiologic mechanisms underlying lower extremity motor recovery in stroke

survivors, such that post-stroke walking rehabilitation is able to effectively target individualized patient deficits and maximize walking ability. The overall objective of this dissertation project was to investigate corticomotor factors underlying lower extremity clinical and biomechanical walking function following stroke and to determine the association between cortical and biomechanical responses to walking rehabilitation. The purpose of this review is to discuss the current evidence of neurophysiologic mechanisms and biomechanical impairments that may influence lower extremity recovery in stroke and implications this may have on rehabilitation approaches.

Background and Significance

Neurophysiologic contributions to lower extremity function post-stroke

Over the past couple of decades, animal and human studies have indicated that the motor cortex is actively and intricately involved in the regulation of walking[5,7,12-15] and that atypical alterations in cortical drive following brain injury contribute to impaired function.[16,17] A non-invasive brain stimulation technique, Transcranial Magnetic Stimulation (TMS), is a technology that has allowed for quantification of the strength of cortical drive from the motor cortex to the muscles in the extremities. Through depolarization of cortical motor neurons, TMS can elicit motor evoked potentials (MEPs) that have the ability to characterize different aspects of corticomotor input that underlie control of the upper and lower extremities.[18] TMS has enhanced our knowledge of neurophysiologic properties in the brain that underlie motor recovery from brain injury in humans.[3,18] Excellent temporal resolution of TMS

techniques has allowed for the study of fast and causal interactions within the cortex and direct connectivity between the central nervous system and muscles. The relatively low cost of a TMS stimulator, quickness of set-up and acquiring measures, and ease of training professionals to collect measures also gives TMS an economic advantage that could enable its potential use in clinical settings.

Though the importance of cortical involvement in the control of lower extremity function is well-established, our understanding of how cortical mechanisms and factors impacting motor recovery following injury to the brain is poor. Neurophysiologic mechanisms underlying upper extremity functional recovery have been well-researched and yielded important information regarding brain processes of recovery post-stroke. TMS studies have consistently observed abnormally small MEP response in the paretic limb during stimulation of the *lesioned* hemisphere in individuals with poor motor recovery[17,19-21] Conversely, during stimulation of the nonlesioned hemisphere, abnormally large MEP responses in the nonparetic limb,[22,23] and ipsilateral corticomotor responses in the paretic limb were observed.[24,25] The resulting hemispheric imbalance and *corticomotor asymmetry* between limbs has been associated with poor upper extremity motor recovery in stroke survivors.[22,23,26,27]

Upper extremity TMS studies have also used sophisticated techniques to measure interhemispheric connectivity through transcollosal pathways in arm and hand cortical motor regions. Findings of this work demonstrated atypically high levels of interhemispheric inhibition from the nonlesioned hemisphere to the lesioned hemisphere that were associated with poor motor recovery of the upper extremity.[28]

Interestingly, this interhemispheric inhibition in stroke has been shown to behave differently during rest than during movement and was shown to be strongest during movement onset of a reaching task in the paretic upper extremity.[24] Rehabilitation techniques that effectively suppressed interhemispheric inhibition from the nonlesioned hemisphere improved functional upper motor outcomes in stroke survivors.[29] Together, prior research has created a neurophysiologic model of decreased excitability and increased inhibition within the lesioned hemisphere coupled with over-activity and disinhibition of the nonlesioned hemisphere in stroke survivors with poor upper extremity function.[20,25,30]

Corticomotor input to the upper extremity has also been shown to be predictive of motor recovery in acute and sub-acute stroke populations[31-33] and functional outcomes in response to intervention in chronic stroke populations.[26] Absence of an MEP in response to TMS in the acute stages following infarct was shown to be predictive of absent or very poor functional hand recovery[31,33] and correlations have been found between MEP amplitude and recovery of upper extremity motor function.[32] In chronic stroke, changes in MEP amplitude asymmetry between paretic and nonparetic hand muscles after a single session of rehabilitation predicted functional improvement in response to a long-term intervention.[26] These insights have enabled the development of TMS as a potential tool to guide rehabilitation efforts for stroke survivors.[34]

The upper extremity model of post-stroke corticomotor adaptations has greatly advanced our knowledge of post-stroke stroke motor recovery. However, there are

differences between the control of the upper and lower extremities that may not allow generalization of this stroke recovery model to be carried over to the lower extremity. Differences in cortical function and organization exist between upper and lower extremities that have created some ambiguity of motor recovery mechanisms in the lower extremity following stroke. The lower extremity is generally not involved in fine motor task performance, has a smaller motor map size with fewer neurons dedicated to innervation, and less strong corticospinal projections than the upper extremity.[35] Some studies have found that activity and ipsilateral projections from the unaffected hemisphere are essential to functional motor recovery for patients with less motor recovery [26,36] and for behaviors involving less cortical input.[37,38] Evolving research in the lower extremity has indicated that cortical remodeling could behave in a similar pattern to that of the upper extremity, with increased corticomotor excitability to the paretic leg from the lesioned hemisphere being related to good functional recovery of independent transfers,[39] walking, and stair climbing.[40] The role of the nonlesioned hemisphere in lower extremity functional recovery has not been thoroughly investigated. Using diffusion tensor imaging techniques and TMS, Madhavan et al found stronger conductivity from the nonlesioned hemisphere to the paretic ankle muscles was related to poor performance accuracy during a simple ankle flexion task.[16] Still, it is unknown how this pattern of corticomotor input relates to more complex functional tasks such as ambulation and if such corticomotor input could potentially predict functional motor recovery of the lower extremity.

Activation of homologous muscles of the nonparetic contralateral extremity is another factor that has been shown to influence motor performance of paretic upper and lower limbs of stroke survivors. A common observation following stroke is that stroke survivors often demonstrate involuntary symmetric movements of the paretic limb during effortful nonparetic limb movement.[41,42] Greater performance in paretic arm movements have been observed when they are performed in-phase simultaneously with the nonparetic arm than when they are performed with the paretic arm in isolation.[43-45] Likewise in the lower extremity, paretic motor performance improves during bilateral in-phase tasks.[46,47] Tseng and Morton demonstrated that muscle activation patterns in the paretic dorsi-and plantarflexors that were related to kinematic performance showed the greatest abnormalities during anti-phase bilateral ankle motor tasks.[48] Together, these findings suggest that muscle activation of the nonparetic limb affects the motor behavior of the paretic limb, likely through corticospinal system projections.[48] If such maladaptive corticospinal projections were active during gait, a motor behavior requiring anti-phase bilateral lower extremity motor coordination, then this could contribute to functional walking deficits in individuals post-stroke. However, no studies to date have directly investigated the differential effect of muscle activation within the paretic and nonparetic limbs on corticomotor input to the lower extremity.

Influence of somatosensory input on motor function post-stroke

Though many human studies have focused specifically on cortical motor areas, there is strong evidence that the reduced corticomotor input to the paretic limb

following stroke is influenced by compromised somatosensory cortical function and atypical afferent pathways from the paretic limb. Interneuronal network interactions between afferent pathways to the somatosensory cortex and efferent pathways within the motor cortex typically result in a balanced pattern of cortical excitation and inhibition that is necessary for motor control in neurologically-intact individuals.[15] A sensory stimulus applied peripherally in the upper extremity at short time intervals preceding a TMS pulse to the contralateral primary motor cortex produces both inhibition through intrahemispheric GABAergic networks[49,50] and facilitation through intrahemispheric neuronal connections between the somatosensory and primary motor cortex that synapse with pyramidal neurons.[14] In the lower extremity, this intracortical afferent input has been shown to be primarily facilitatory in nature for both dorsiflexor and plantarflexor muscles.[15]

Atypical interhemispheric interactions observed in stroke survivors can also be strongly influenced by sensorimotor function. When somatosensory cortical function is compromised following stroke, this likely indirectly contributes to the observed disinhibition of the nonlesioned hemisphere.[51] Depriving one hemisphere of somatosensory input through deafferentation of the upper extremity in neurologically-intact humans resulted in decreased corticomotor excitability of the contralateral primary motor cortical area that provided innervation to the corresponding muscles.[52,53] Additionally, increased ipsilateral corticomotor excitability in homologous muscles contralateral to the deafferented limb were observed, likely resulting from decreased interhemispheric inhibition.[54] In stroke, blocking afferent

input from the nonparetic arm also increased the corticomotor excitability of paretic arm and hand muscles from the lesioned hemisphere and improved somatosensory discrimination and motor performance.[55] Likewise, increased afferent input to one hemisphere was shown to have an *inhibitory* effect on the contralateral hemisphere.[51] There is limited evidence on the effect of afferent input on interhemispheric interactions in the lower extremities. Jayaram and Stinear applied an intervention using inhibitory peripheral stimulation to the nonparetic lower extremity and found that it increased corticomotor excitability of the paretic tibialis anterior during gait.[56] To date, research has indicated that somatosensory input from one limb can largely influence motor cortical activity and strength of corticomotor pathways of both the hemispheres and manipulating this afferent input can affect motor performance.

Therapeutic techniques that manipulate somatosensory input to both the paretic and nonparetic limbs have been shown to induce neuroplasticity and enhance motor performance in individuals with stroke. Alteration of afferent input through prolonged peripheral nerve stimulation can produce changes in the primary motor cortex and enhance corticomotor excitability to upper extremity muscles.[57,58] Post-stroke rehabilitation strategies such as constraint induced movement therapy and the use of functional electrical stimulation (FES), that target impairments of sensorimotor function, have demonstrated an increase in corticomotor input from the lesioned hemisphere to paretic upper extremity muscles that is related to improved function.[59-63] Responses to these rehabilitation strategies can be observed at all time periods, from days to years, following stroke[60-63] and have been shown to be retained for at least 2

years after the intervention.[59] For the lower extremity, rehabilitation strategies operating on these neurophysiologic principles present a number of challenges, as both legs are used simultaneously for most functional activities such as walking. However, it is possible that the development of feasible rehabilitation strategies that target neurophysiological deficits in these patients could translate to optimal motor recovery of the lower extremity.

Biomechanical contributions to lower extremity function post-stroke

The inability to efficiently activate paretic limb muscles during gait can lead to ineffective and inefficient walking patterns, as observed in stroke survivors with lower limb hemiparesis.[64] As a result, many individuals utilize inefficient compensation strategies, such as stiff-legged and circumduction gait to advance the affected limb[65,66] to regain walking independence as quickly as possible.[67] Our lab recently showed that compensation strategies can increase the energy cost of walking,[68] which may limit gait speed and endurance in these individuals following stroke, decreasing their maximal potential functional recovery. A number of paretic lower extremity strength and biomechanical measures have been shown to be related to post-stroke walking function, including dorsiflexor muscle strength[69,70] and propulsive force generating ability.[71-74] Propulsive force generated by the paretic lower extremity has been identified by a number of studies to be perhaps the *most* significant contributor to walking speed impairments and can determine whether an individual is functionally categorized as a limited community or community ambulator.[9,75] Another important functional indicator following stroke is the ability to modulate reduced walking

speeds. Impaired paretic ankle power generation of the paretic limb was shown to limit walking speed modulation in stroke survivors.[76] Recently, improvements in biomechanical contributions of paretic limb propulsion were shown to improve post-stroke walking function.[77,78] However, the factors limiting these biomechanical determinants of post-stroke gait are unclear. It is conceivable that neurophysiologic measures of corticomotor excitability could yield information about neural substrates and the potential for individuals to improve utilization of specific biomechanical strategies during gait. The relationship between corticomotor and biomechanical measures of the lower extremity has not been investigated, despite the importance that such understanding could have in optimizing functional recovery.

Impairments in inter-limb coordination patterns post-stroke are also related to stance-phase paretic limb gait deficits.[79] In addition to increased abnormal EMG activity of ankle dorsi- and plantarflexor muscles, poor performance during anti-phasic lower extremity movement tasks have been related to poor walking performance.[47] This suggests that activation of the nonparetic leg muscles may impede performance of the paretic leg during gait, specifically during the critical late stance phase period when the highest propulsion forces are typically generated to advance the center of mass and the paretic limb forward.[79] Despite the importance to post-stroke gait biomechanics, neurophysiologic mechanisms underlying inter-limb activation deficits in the lower extremity are largely unknown.

Neurophysiologic measures of corticomotor input to the lower extremity could provide critical insight into central nervous system mechanisms underlying poor lower

extremity neuromuscular control in stroke survivors. Improvements in such neurophysiologic measures could translate into more efficient post-stroke gait patterns. Clinicians could become empowered to implement rehabilitation strategies that optimize walking recovery by effectively improving lower extremity neural function.

Effect of rehabilitation on neurophysiologic and biomechanical function post-stroke

It is clear that changes in brain structure and function accompany gains in motor function following stroke,[60] but it is unknown which rehabilitation strategies are the most effective in making these changes and what prognostic criteria could allow us to predict who will respond to specific rehabilitation strategies and who will not. Additionally, it is well-established that improvements in biomechanical contributions of the paretic limb are related to gains in lower extremity function. However, most rehabilitation programs address muscle strengthening, cardiovascular fitness, balance and joint range of motion,[80] and have failed to address sensorimotor function of the paretic limb. These rehabilitation strategies do not sufficiently target the function of the paretic limb and generally lead to strengthening of compensation strategies instead of learning to utilize more optimal gait patterns, limiting functional outcomes.[81,82] Reliance on AFOs or assistive devices immobilizes the paretic leg and increases the reliance on the nonparetic leg, further contributing to decreased use of paretic limb function. Decreased reliance on the paretic leg and increased reliance on the nonparetic leg has been shown to be related to major neuronal synaptogenesis and reorganization in the unaffected hemisphere following unilateral cerebral injury.[3] Even

in neurologically-intact individuals, coupling immobilization and non-use of one extremity with heavy reliance on the contralateral extremity for functional tasks results in hemispheric imbalances of cortical excitation and inhibition.[83] Likewise, learning of new motor skills triggers increased corticomotor excitability that enhances the potential for long-term neuroplasticity underlying improved performance.[84,85] It is conceivable that individuals with poor motor recovery may utilize compensation strategies in the early phases of recovery that induce neuronal changes associated with poor motor recovery, causing them to be unable to gain full recovery of the paretic leg. Rehabilitation strategies that implement increased utilization of compensation strategies could promote maladaptive neurophysiologic changes that translate to poor functional recovery. Interventions utilizing strategies that target motor and somatosensory deficits in the paretic limb could potentially decrease use of compensations and promote use of the paretic leg, which may optimize outcomes in some patients.

Effect of functional electrical stimulation on neuroplasticity and motor function

Although strategies targeting motor and somatosensory deficits such as constraint induced movement therapy used in the upper extremity are effective, implementation of the same strategies may not be practical or feasible for the lower extremity. However, other strategies may be used to improve motor impairments of the lower extremity post-stroke. Functional electrical stimulation (FES) is a rehabilitation strategy that temporally couples stimulation of motor nerve fibers and sensory afferent fibers during performance of a specific motor task. Perceptual

information of the electrically evoked movement during a meaningful and functionally relevant task can further enhance motor learning.[3,86] Rushton posited that antidromic FES-triggered discharge occurring simultaneously with voluntary movement leads to synchronization of pre- and postsynaptic firing of the pyramidal tract and anterior horn cells that enhanced synaptic remodeling.[87] Though the precise mechanism underlying neural network changes with this temporally-coupled sensorimotor integration have yet to be elucidated, the use of FES in rehabilitation has been shown to facilitate neuroplasticity and improve functional outcomes in the upper and lower extremities.[61-63] A number of studies have concluded that the use of paretic limb FES during rehabilitation activities changed cortical activation patterns that were associated with improved clinical function of the upper extremity [61-63,88] Functional MRI studies showed that in patients with improved functional motor control following rehabilitation interventions utilizing FES, there was a decrease in unaffected hemisphere activation[62,63] and a shift in the focus of brain activity to the affected somatosensory cortex[61] during a paretic hand motor task. FES to the dorsiflexor muscles of the paretic lower extremity during gait also improved timing of muscle activation in the dorsiflexors[89] and increased corticomotor excitability to the paretic dorsiflexor muscles in response to long-term intervention.[90] Findings in neurologically-intact individuals indicated that FES in conjunction with voluntary task-specific muscle contraction was more effective than sensory stimulation alone to induce cortical excitability and plasticity.[91,92] Christiansen et al found that even when removing the effect of conscious perception of sensory stimulation through a peripheral ischemic nerve block, activation of the somatosensory cortex was still observed through fMRI during voluntary FES assisted movements,[93] indicating that

the neuroplastic effects of FES are not completely dependent on intact sensation of the limb, as observed in stroke survivors. Further, an fMRI study by Gandolla et al demonstrated that FES coupled with voluntary dorsiflexion increased the sensitivity of the primary somatosensory cortex selectively to primary motor cortex projections,[94] providing further evidence of the effect of FES on corticomotor control in the lower extremity. However, no studies to date have investigated the neurophysiologic effect of FES delivered to the plantarflexor muscles to target paretic leg propulsion, one of the major contributing impairments to gait dysfunction.[71-74,95] A recent literature review of the use of FES to lower extremity muscles in individuals post-stroke concluded that compared to matched treatments, FES was *not* superior in enhancing functional ambulation improvements, creating further ambiguity on the effectiveness of FES in inducing neuroplasticity and resulting motor learning coupled with biomechanical changes.[96]

Though targeting improvements in the paretic limb's contributions to walking ability through the use of an intervention such as FES may be an effective treatment strategy for some patients, it is unlikely to be the optimal strategy for all patients. For example, Page et al[97] observed an *opposite* change in cortical activation patterns in participants with versus without active extension of the fingers or wrist. The individuals with the most severe motor impairments actually showed an *increase* in activity of the nonlesioned sensorimotor cortex and no clinically significant improvements in motor function in response to an intervention with FES.[97] Discrepancies of patterns of corticomotor changes and upper extremity motor improvements between patients with low-level[97] versus higher-level functional ability[61-63] suggest that a neural substrate that enables some voluntary activation of the

paretic extremity muscles may be essential to make functional motor gains of the paretic limb.[98] Although gait training with FES has the potential to induce neuroplasticity that could translate into robust functional gains, it is possible that this rehabilitation strategy may not be effective for all patients. Thus, it is important to identify prognostic criteria for individual patient response to specific rehabilitation strategies.

Amongst a heterogeneous patient population, our ability to predict those patients who have the capacity to improve paretic limb contribution to walking function is poor. Currently, rehabilitation specialists have no reliable and consistent clinical test or tool to predict those who would respond to specific motor retraining strategies versus those who would benefit more from compensatory training for the best functional outcomes. Objective measures of corticomotor pathways to targeted muscles performed prior to an intervention have the potential to help us determine those who would benefit most from a specific rehabilitation strategy.[99] In fact, measures of changes in corticomotor excitability in response to a single training session were shown to offer good predictive ability to patients who will respond to interventions. Corticomotor responses to a single session of motor activity in the upper extremity can be detected in both low and high-level patients[29] and these responses have been shown to predict functional outcomes after 4 weeks of treatment.[26] Neurophysiologic responses to different types of treatments could be compared to determine the best strategy for each individual, enabling clinicians to individualize treatment and spending little time on less efficient treatment approaches.

Specific Aims and Hypotheses

The overall objective of this dissertation project was to investigate corticomotor factors underlying lower extremity clinical and biomechanical walking function following stroke and to determine the association between FES-induced cortical and biomechanical responses to walking rehabilitation. Based on previously published research and preliminary data from our laboratory, we hypothesized that corticomotor input to the dorsi- and plantarflexor muscles would influence post-stroke clinical function and biomechanical walking impairments and could be modified through gait training with FES targeting specific impairments. We tested our hypotheses and objectives by pursuing the following three specific aims:

<u>Aim 1:</u> To compare corticomotor input to the lower extremity in individuals with chronic stroke who demonstrate good versus poor recovery of walking function and neurologically-intact controls.

Previous research in the upper extremity has provided strong and consistent evidence to indicate that *decreased* corticomotor input from the *lesioned* hemisphere[17,20,21,30] and *increased* corticomotor input from the *nonlesioned* hemisphere to the paretic arm and hand are associated with poor functional recovery post-stroke.[24,25] This hemispheric imbalance increases during muscle activation altering corticomotor input to paretic muscles to a greater degree than at rest, a finding not observed in neurologically-intact controls.[24,100] This aim determined if similar corticomotor patterns were present within the lower extremity of stroke survivors and the effect of muscle activation on corticomotor input to the lower extremity.

H1.1. Corticomotor symmetry between paretic and nonparetic lower extremity muscles will be different in individuals with poor versus good post-stroke walking recovery and neurologically-intact controls.

H1.1.1. Corticomotor symmetry will be different in resting versus active motor states in individuals with poor versus good walking recovery following stroke.

H1.1.2. Atypical patterns of corticomotor input will be greater in plantarflexors than dorsiflexors in individuals with poor versus good walking recovery following stroke.

H1.2. During activation of the nonparetic lower limb, there will be altered corticomotor drive to the paretic lower limb muscles in stroke survivors with poor versus good walking recovery.

<u>Aim 2:</u> To determine the influence of corticomotor drive to the lower extremity on biomechanical strategies to achieve an individual's level of walking function in the chronic stage of stroke.

In the presence of lost function following brain injury, one of the most common and consistent observations is that individuals develop compensatory strategies to perform daily activities such as walking.[3,29] Such compensations are related to major changes in synaptogenesis and neural remodeling in both cortical

hemispheres.[83,101] This aim determined if atypical neurophysiologic measures observed in Aim 1 were related to kinetic and kinematic measures during gait in stroke survivors.

H2.1. There will be a positive relationship between plantarflexor corticomotor symmetry and change in plantarflexion ankle moment symmetry with change in walking speed in individuals with chronic stroke.

H2.2. Corticomotor symmetry to plantarflexor muscles will moderate the relationship between change in plantarflexion ankle moment symmetry and walking speed modulation in individuals with chronic stroke.

H2.3. Corticomotor drive to the paretic tibialis anterior will be related to dorsiflexion angle during gait in individuals with chronic stroke.

Aim 3: To determine the relationships between changes in corticomotor excitability to lower extremity muscles and changes in walking biomechanics in response to a single session of gait rehabilitation using functional electrical stimulation in individuals with chronic stroke.

The purpose of this aim was to determine whether atypical corticomotor drive related to poor lower extremity function (Aim 1) and biomechanical measures (Aim 2) could be changed in response to a session of rehabilitation. The use of FES has been

shown to induce positive neuroplastic changes when coupled with voluntary task-specific movement.[91,92,94,102]. This aim sought to identify short-term changes in corticomotor input to the lower extremity that could be effectively induced with rehabilitation and determined if they were related to biomechanical changes in response to gait training with FES to dorsi- and plantarflexor muscles.

H3.1. Improvements in corticomotor symmetry to the plantarflexor muscles and plantarflexor ankle moment symmetry will be greater following a session gait training with FES than a session of gait training without FES in stroke survivors.

H3.2. Changes in corticomotor drive to plantarflexor muscles will be related to changes in ankle moment during walking following gait training with FES in stroke survivors.

H3.3. A session of gait training with FES will reduce atypical corticomotor drive to the paretic dorsiflexors during nonparetic lower limb muscle activation in stroke survivors.

H3.3.1. Changes in atypical corticomotor drive to paretic dorsiflexors will be related to changes in paretic dorsiflexion ankle angle during walking following gait training with FES.

H3.3.2. Changes in atypical corticomotor drive to paretic dorsiflexors will be related to changes in paretic plantarflexion ankle moment during walking following gait training with FES.

Chapter 2

CHARACTERIZING DIFFERENTIAL POST-STROKE CORTICOMOTOR DRIVE TO THE DORSI- AND PLANTARFLEXOR MUSCLES DURING RESTING AND VOLITIONAL MUSCLE ACTIVATION

Abstract

Objective: Corticomotor input to paretic and nonparetic hands, as measured by transcranial magnetic stimulation (TMS), has been shown to be different in stroke survivors and neurologically-intact controls, and imbalance of corticomotor input between hemispheres has been associated with the extent of upper extremity motor recovery post-stroke. As largely indicated by upper extremity research, corticomotor excitability is greatly influenced by specific testing conditions, such as the presence or absence of volitional muscle activation, and may vary across muscle groups. However, post-stroke corticomotor drive to lower extremity muscles has not been thoroughly investigated. The purpose of this study was to compare corticomotor excitability of the dorsi- and plantarflexor muscles during resting and active conditions in individuals with good and poor post-stroke walking recovery and neurologically-intact controls.

Methods: In twenty-nine individuals post-stroke (16 fast-walkers, 13 slow-walkers) and 14 neurologically-intact individuals, TMS targeting the tibialis anterior (TA) and soleus muscles was delivered during conditions of rest and voluntary muscle contraction. Average motor evoked potential (MEP) amplitudes for each muscle were calculated for the resting and active conditions. Corticomotor symmetry was

calculated as the ratio of the average paretic (non-dominant) divided by the non-paretic (dominant) MEP amplitude for each muscle during each condition.

Results: Both the fast-walking and slow-walking stroke subjects showed improvements in dorsiflexor corticomotor symmetry during the active versus resting condition (fast, p=.01, slow, p=.02) while the control group showed no differences between conditions. Plantarflexor corticomotor symmetry showed no difference between resting or active conditions in any group. During the active condition, dorsiflexor corticomotor symmetry was greater than plantarflexor corticomotor symmetry (p=.04). Reduced plantarflexor corticomotor symmetry in the active condition was a result of reduced corticomotor drive to the paretic muscles and enhanced corticomotor drive to the nonparetic muscles versus the neurologically-intact subjects. The pattern of reduced corticomotor symmetry in plantarflexors versus dorsiflexors was most exaggerated in the slow-stroke group.

Conclusions: Results indicate that during active muscle contraction, corticomotor drive to paretic and nonparetic plantarflexor muscles is more severely affected than corticomotor drive to the dorsiflexor muscles in stroke survivors. Stroke survivors with poor walking recovery demonstrated both reduced corticomotor drive to the paretic limb and greater corticomotor drive to the nonparetic limb when compared to neurologically-intact controls.

Significance: Future studies are needed to determine if rehabilitation strategies that promote corticomotor balance to plantarflexor muscles could translate to improvements in post-stroke walking function.

Introduction

Despite intensive rehabilitation efforts, the majority of stroke survivors are unable to recover walking ability to allow safe and effective community function.[103,104] Previous research conducted largely on upper limb muscles shows that ischemic loss of neurons combined with maladaptive cortical reorganization underlies post-stroke functional impairments.[105] Although the motor cortex plays an important role in the control of human ambulation,[5,7] there are substantial gaps in our understanding of the cortical mechanisms underlying the neural control of lower limb muscles and walking ability in stroke survivors. During post-stroke motor recovery, there is an increased adaptive neuroplastic capacity that has not been adequately characterized and has created a barrier for current rehabilitation approaches. Further, there is a disconnect between our knowledge of the primary muscle groups that biomechanically limit post-stroke walking function and our understanding of the neural mechanisms underlying motor control of these muscles. Understanding post-stroke neural recovery mechanisms and determinants of walking function is imperative to advance the effectiveness of rehabilitation strategies and maximize positive neuroplastic changes during lower extremity motor recovery.

As consistently demonstrated by animal and human models, widespread neural synaptogenesis and remodeling occurs following stroke. During the process of motor recovery, changes in cortical network activity patterns occur in both the lesioned and nonlesioned hemisphere, both of which play a critical role in upper extremity motor

function.[106-108] A decrease in cortical activity in the lesioned sensorimotor cortex[109] and decreased corticomotor excitability of paretic arm and hand muscles from the lesioned primary motor cortex are related to poor motor function and have been well-established in previous literature.[17,19-21,30] Interestingly, an increase in nonlesioned motor cortical activity,[109] strengthening of ipsilateral corticomotor pathways from the nonlesioned motor cortex,[20,25,110] and enhanced corticomotor excitability of the nonparetic upper extremity[22,23] have also been observed in stroke survivors. Studies investigating post-stroke interhemispheric connectivity reveal that the level of disinhibition from the lesioned to the nonlesioned hemisphere was related to the level of post-stroke motor impairment.[24,111] In turn, disinhibition of inhibitory transcallosal pathways from the nonlesioned to the lesioned hemisphere further suppressed corticomotor excitability of the paretic limb.[112,113] Together, this evidence provides a neurorecovery model of suppressed lesioned hemisphere excitation coupled with enhanced nonlesioned hemisphere excitability. This model provides further explanation for the *asymmetry of corticomotor input* to paretic and nonparetic limbs documented in stroke survivors that is associated with poor motor recovery in the upper extremity.[23,27,109] Evolving research in the lower extremity has indicated that, similar to the upper extremity, reduced corticomotor excitability to the paretic limb is related to lower extremity clinical function of transfers[39] and walking.[40] Other studies using neuroimaging techniques showed that stronger ipsilateral conductivity from the nonlesioned hemisphere to the paretic leg was related to greater lower extremity motor impairment.[16,114] However, corticomotor input from the nonlesioned hemisphere to the

nonparetic lower limb that can also influence corticomotor symmetry has not been thoroughly investigated. Considering the complex interlimb coordination patterns necessary for walking, information about corticomotor function of the nonparetic limb could be critical towards our understanding of lower limb motor recovery and development of rehabilitation strategies to maximize post-stroke walking function.

Mechanisms of interhemispheric interactions between primary motor cortices that can influence corticomotor symmetry between limbs behave differently during resting versus active motor states.[24,110,115] Typically, during volitional muscle contraction, motor evoked potential (MEP) responses to transcranial magnetic stimulation (TMS) in the contracted muscle are enhanced from the resting state.[116] Studies using fMRI have shown that, during submaximal isometric contraction, activation of the contralateral primary motor cortex increases in neurologically-intact individuals while activation of the ipsilateral hemisphere is only present during high effort levels or complex functional tasks.[117,118] However, alterations in these typical patterns of corticomotor input and cortical activity have been observed in stroke survivors. Previous studies revealed that individuals with poor motor recovery showed activation of the ipsilateral nonlesioned motor cortex during simple submaximal paretic hand movements, a finding not observed in neurologically-intact controls.[119-122] In addition, during paretic upper limb muscle activation, atypical interhemispheric interactions from the nonlesioned to the lesioned upper limb primary motor cortical areas have been reported in stroke survivors with poor motor function.[24] In contrast to neurologically-intact individuals, transcallosal inhibition from the nonlesioned to the

lesioned hemisphere increased in individuals with chronic stroke during movement.[24] These atypical interhemispheric interactions are believed to be one source of the muscle activation deficits contributing to poor motor function in stroke survivors.[24,51,123] Interestingly, these interhemispheric interactions do not appear to be abnormal during resting states in the same stroke survivors.[24,100] It is conceivable that similar atypical interhemispheric interactions during an active motor state may play a role in the lower extremity motor recovery and could affect interlimb coordination during walking.[124] The close proximity of neuroanatomical locations of lower extremity primary motor cortical representations to the medial longitudinal fissure presents challenges for measuring interhemispheric interactions in the lower extremity using similar methods to those used in the upper extremity.[125] Still, comparisons of corticomotor asymmetry between paretic and nonparetic lower limbs during different conditions of active versus resting motor states could shed some light on cortical mechanisms that occur with lower extremity muscle contraction.

Fundamental differences in the strength of cortical input between the dorsiflexor muscles and other lower extremity muscles are well-established in neurologically-intact individuals.[5-7] Larger MEP amplitudes in response to TMS in the tibialis anterior (TA) than other lower extremity muscles suggest that this muscle receives stronger corticomotor input from the primary motor cortex.[7] It has been postulated that the dorsiflexors may be the lower extremity muscle most affected by stroke resulting in the commonly observed clinical impairment of "foot drop" in the paretic limb of stroke survivors.[126] Thus, the focus of current clinical and research

efforts have been to remediate or compensate for impairments in paretic dorsiflexion believed to limit post-stroke walking function.[126-128] However, contemporary biomechanical literature has indicated that dorsiflexion impairments and "foot drop" are not limiters of post-stroke gait speed.[129] Rather, plantarflexor impairments and deficits in paretic limb propulsion[9,71,129] and paretic ankle power generation[130] are the primary limiters of post-stroke walking function. Effective improvement of paretic limb propulsion through rehabilitation has enhanced walking ability in stroke survivors beyond that of contemporary rehabilitation.[77] Despite the strong and consistent evidence of these critical impairments in propulsion to post-stroke walking function, neurophysiologic research to date has focused on motor control of dorsiflexors[16,131] and has failed to characterize the cortical mechanisms underlying plantarflexor motor control in stroke survivors. The lack of understanding of the neural mechanisms underlying plantarflexion motor recovery has created a disconnect between the neuronal and biomechanical factors that limit post-stroke walking ability. The objectives of this study were to 1) determine the effect of active versus resting motor states on lower limb corticomotor asymmetry in stroke survivors with good and poor levels of walking recovery and neurologically-intact individuals 2) compare the corticomotor excitability of dorsiflexor versus plantarflexor muscles in stroke survivors with good and poor levels of walking recovery and neurologically-intact controls and 3) investigate the contribution of nonparetic limb corticomotor input to corticomotor asymmetry in stroke survivors with good and poor levels of walking recovery and neurologically-intact controls. We hypothesized that (H1) corticomotor

asymmetry between paretic and nonparetic lower limbs in active versus resting motor states would be different in individuals post-stroke versus neurologically-intact controls, (H2) atypical patterns of corticomotor input would be greater in plantarflexor than dorsiflexor muscles and (H3) nonparetic corticomotor drive would be greater in individuals with poor post-stroke walking recovery than individuals with good post-stroke walking recovery and neurologically-intact controls.

Methods

A cross-sectional study design was used. Independent variables were group (fast-walkers, slow-walkers, control), condition (active and resting), limb (stroke: paretic and nonparetic, controls: nondominant and dominant) and muscle (TA and soleus). Dependent variables were mean peak-to-peak motor evoked potential (MEP) amplitude at 100% stimulator intensity (MEP_{100}) measured with transcranial magnetic stimulation (TMS) and corticomotor symmetry between paretic (nondominant) and nonparetic (dominant) limb MEP amplitude. Twenty-nine individuals with chronic stroke (> 6 mo.) and 14 neurologically-intact individuals participated in this study (Table 1). The stroke group was dichotomized into fast-walking ($\geq$0.8m/s) (n=16) and slow-walking (<0.8m/s) (n=13) groups using an average measure of three trials of a self-selected 10-meter walk test, as previously described.[115] This 0.8m/s cut-off speed was used because previous research has established that a self-selected walking speed of 0.8m/s is necessary for unrestricted community ambulation in the stroke patient

population.[75,132] All participants gave written informed consent and the experimental protocol was approved by the University of Delaware's Institutional Review Board. All participants in the stroke groups had lower extremity hemiparesis with visually detectable gait deficits, sustained a single cortical or subcortical stroke, and were able to walk a distance of >10 m without an orthotic and without the assistance of another person. Participants were excluded if they had sustained >1 previous stroke, cerebellar involvement, pain in the lower extremities, and any contra-indications affecting the safety of TMS.[133] All participants in the neurologically-intact control group had no history of neurologic pathology or any unsafe TMS testing criteria.[133] Lower limb dominance of the control participants was determined as the preferred foot to kick a ball.[134]

Assessment of Corticomotor Excitability

A magnetic stimulator (Magstim 200^2, MagStim Ltd., Wales, UK) was used to deliver monophasic magnetic pulses with a 100μs approximate rise time and a 1.0ms total duration through a custom batwing coil (maximal output 2 Tesla, each wing 11 cm in diameter, angle between windings 65˚). All participants were seated upright in an arm chair with both feet resting on the floor and knees and ankles positioned at approximately 90 degrees. EMG activity was recorded from double differential surface electrodes with integrated ground (BL-AE, B&L Engineering, Santa Ana, CA) that were carefully positioned and secured to the skin over the lateral soleus and tibialis anterior (TA) muscles of the paretic and nonparetic legs using a 6 channel active EMG system (BL-EMG-6, B&L Engineering, Santa Ana, CA). EMG data were

sampled at a rate of 2000Hz with a 330 gain set on a 16 bit data acquisition board (National Instruments NI USB-6341) and band-pass filtered at 15-450 Hz. The coil was aligned posterior-anteriorly and parallel to the interhemispheric fissure so that the induced electrical current traveled in the anterior direction within the cortex.[135] The coil was positioned at the vertex of the skull and stimulation began at sub-threshold intensity and gradually increased to an intensity where a visible motor evoked potential (MEP) was observed on real-time EMG within the TA on the targeted side. Suprathreshold magnetic stimuli were delivered while the coil was moved over the scalp and the experimenter searched for the lower extremity "hotspot," the optimal coil position for eliciting MEPs of the greatest amplitude at a given stimulus intensity. During location of the hotspot, participants were asked to maintain a light dorsiflexion contraction of the targeted leg while real-time EMG and MEPs from the TA were visually observed.[115] The hotspot was determined to be the location that elicited MEPs of greatest amplitude within the targeted muscle. Typically, 20-30 stimuli were applied during the search for the hotspot for each muscle. We detected no discernable difference in hotspot locations between the TA and soleus muscles of the same leg regardless of group in our pilot testing for this study. Thus, we chose to use the TA as a guide in the search for the common TA and soleus lower extremity hotspot for each leg because TA MEPs were more pronounced than soleus MEPs, particularly in the slow-walking stroke group.

The experimenter identified and carefully marked the hotspot location for each the paretic and nonparetic lower extremity on the tight fitted cap worn by the

participant. Custom LabVIEW software (National Instruments, Austin, TX) was used to trigger TMS pulses and EMG collection. Data were collected during resting and active conditions. During the active condition, participants were asked to maintain either a light dorsiflexion or plantarflexion contraction at 15% of their maximal volitional TA or soleus EMG activity (Figure 2-1). Participants were provided real-time visual EMG biofeedback to assist them in maintaining a constant level of muscle activity. If a participant was unable to produce or maintain a 15% contraction (i.e. the paretic limb of a severely impaired individual in the stroke group), they were asked to produce an observable increase in EMG compared to the resting EMG activation level that they could maintain. Participants were encouraged to rest if they reported fatigue or if the experimenter detected a change in muscle activity during the trial. A stimulus-response curve was produced from application of TMS pulses at a frequency of 0.2 Hz at intervals of 3% of the stimulator's output intensity from subthreshold through 100% maximum output intensity.[136,137] An additional 10 pulses were delivered at 100% maximum stimulator output intensity to each muscle. Only MEP responses to 100% of the maximum the stimulator's output are presented here.

The maximal response to peripheral nerve stimulation (Mmax) of the tibial and common peroneal nerves was used to normalize MEP amplitudes for the soleus and TA muscles, respectively. The experimenter located the tibial nerve within the popliteal fossa and confirmed the soleus muscle response to peripheral nerve electrical stimulation. A custom electrical stimulator delivered 1 ms square electrical pulses of gradually increasing intensities directly to the nerve until no increase in the M-wave

was observed within the soleus muscle. Next, the common peroneal nerve was located at the level of the fibular head and the same procedures were repeated to acquire the Mmax of the TA muscle. The same testing procedures were performed for the paretic (nondominant) and nonparetic (dominant) legs of all participants.

Data Reduction and Analyses:

We measured pre-stimulus EMG from TA and soleus muscles bilaterally during each condition to ensure that all subjects maintained appropriate EMG activity during each condition (active and resting). The root-mean squared of the pre-stimulus EMG was calculated during a 100ms window prior to the stimulus artifact for each MEP used for analysis.[138] Resting condition trials were discarded from analysis if the contralateral and/or ipsilateral muscle pre-stimulus EMG activity was greater than 10μV and/or showed a visual increase in EMG activity from baseline. Active condition trials were discarded from analysis if the EMG activity of the active muscle was not at least 15μV in amplitude *and* 2.5 standard deviations greater than the resting condition and/or EMG activity in the contralateral muscle was greater than that allowed during the resting condition (10μV). Additionally, active condition trials were discarded if EMG activity in the active limb was 2.5 standard deviations greater than the mean EMG activity of the trial. For the active condition, raw pre-stimulus EMG values of each muscle for all subject groups and pre-stimulus EMG values normalized to maximum EMG activity during a maximum volitional contraction of each muscle are shown for a select number of subjects in each group in Appendix A (see Figure A-1).

MEP amplitude was quantified as the peak-to-peak value of the EMG response within a 100ms window duration beginning at 10ms post stimulus artifact. Using this method, MEP amplitude was a continuous variable, as previously detailed.[139] For each participant, an average of 8-13 normalized, peak-to-peak MEP amplitudes at 100% of the magnetic stimulator output intensity (MEP_{100}) was determined for each the paretic and nonparetic muscles. The average MEP_{100} measure showed good reliability in our pilot testing within individuals ($ICC_{3,k} = 0.962$) (see Appendix B, Table B-1). Corticomotor symmetry between limbs was calculated for the TA and soleus muscles as the paretic limb MEP_{100} divided by the nonparetic limb MEP_{100}. A value of 1.0 indicates perfect symmetry, with the paretic and nonparetic MEP values being equal in magnitude; a value greater than 1 indicates the paretic MEPs were greater than the nonparetic; a value less than 1.0 indicates the paretic MEPs were smaller than the nonparetic.[139]

A 3x2 mixed design analysis of variance (ANOVA) test was used to test if corticomotor symmetry of each group (fast-stroke, slow-stroke, control) differed between condition (active or resting) for either the TA or soleus muscles and to test if corticomotor symmetry of each group differed between muscles (TA or soleus) for either the active or resting conditions. Whenever between-muscle corticomotor symmetry differences were observed, differences in paretic and nonparetic MEP_{100} between groups were tested using a mixed design ANOVA. For all significant interactions, post-hoc testing using a Bonferroni method was performed. If interactions were not significant, main effects were tested. If there were significant

main effects of group, post-hoc testing using a Bonferroni method was performed. All analyses were performed using SPSS version 23 with α set to 0.05.

Results

Optimal coil positions for the hotspot were measured for each group. Relative to the vertex of the skull, coil locations used for testing the paretic limb were on average 2.0±0.4cm lateral and 1.3±0.5cm anterior and the nonparetic limb were 2.3±0.4cm lateral and 1.3±0.8cm anterior for all groups. There was no difference in coil location between groups for either limb in either direction (paretic: lateral p=.32, anterior p=.48) (nonparetic: lateral p=.42, anterior p=.56).

Complete data sets were collected for all participants in the stroke groups. Resting MEPs in the nondominant lower extremity were not collected for one participant in the control group due to time constraints of the testing session, and this participant was discarded from all resting MEP analyses. All MEP_{100} data met assumptions of normality, sphericity, and heteroscedasticity. A 3x2 mixed design analysis of variance (ANOVA) was used to test if corticomotor symmetry of each group (fast-stroke, slow-stroke, control) differed between condition (active or resting) for either the dorsiflexor or plantarflexor muscles. There was a significant group by condition interaction for dorsiflexor corticomotor symmetry ($F_{2,39}$=3.71) (p=.03). Dorsiflexor corticomotor symmetry was greater during the active condition than during rest in the fast-stroke (p=.02) and slow-stroke groups (p=.02) but not in

controls. No group by condition interaction was observed for the plantarflexor corticomotor symmetry ($F_{2,39}$=0.75) (p=.48). There was a significant main effect of group ($F_{2,39}$=23.53) (p<.01) but not condition. Plantarflexor corticomotor symmetry was lesser in the slow-stroke group than the fast-stroke (p=.01) and the controls (p<.01). The fast-stroke group also had lesser plantarflexor corticomotor symmetry than controls (p<.01).

We used a 3x2 mixed ANOVA to test if corticomotor symmetry of each group differed between muscles (TA or soleus) for either the active or resting conditions. During the active condition, no significant interaction was observed between group and muscle for corticomotor symmetry ($F_{2,40}$=2.44) (p=.10) but there were main effects of muscle ($F_{1,40}$ =4.14) (p=.04) and group ($F_{2,40}$ =14.23) (p<.01) (see Figure 2-2). Corticomotor symmetry was significantly greater in the TA than the soleus muscle (p=.04) (see Figure 2-3 for representative subject). The control group had greater corticomotor symmetry than fast (p<.01) or slow stroke groups (p<.01). The fast-stroke group had greater corticomotor symmetry than the slow-stroke group (p=.03). During the resting condition, there was no significant muscle by group interaction ($F_{2,39}$ =0.03) (p=.97). A significant main effect of group ($F_{2,39}$ =29.13) (p<.01) but not muscle ($F_{1,39}$ =0.04) (p=.835) was observed. The control group had greater corticomotor symmetry than fast (p<.01) or slow stroke groups (p<.01). The fast-stroke group had greater corticomotor symmetry than the slow-stroke group (p=.02).

Because there was an effect of muscle in the active condition, we broke apart the symmetry measure into the components from the paretic and nonparetic limbs to

further examine whether the nonparetic side contributed to the asymmetries in the active condition. Tests of interlimb differences in corticomotor excitability between muscles were performed using a 3x2 mixed design ANOVA. Specifically, we tested if MEP_{100} for each group differed between limbs (paretic or nonparetic) for either the TA or soleus muscles during the active condition. For the soleus muscle, there was a significant group by limb interaction for the MEP_{100} ($F_{2,40}$=15.64) (p<.01) (Figure 2-4). Between-group pairwise post hoc comparisons revealed that soleus MEP_{100} in the nondominant limb in controls was greater than the paretic limb for the slow-stroke (p<.01) and fast-stroke groups (p=.01). Soleus MEP_{100} in the paretic limb was not different between the fast versus slow-stroke group (p=.21). Soleus MEP_{100} in the nonparetic limb was greater in slow-stroke than controls (p=.01) and trended towards significance versus the fast-stroke group (p=.11) (Figure 2-4). Nonparetic soleus MEP100 was not different between the fast-stroke and the control group (p=.20). Within group comparisons showed that the nonparetic (dominant) soleus MEP_{100} was greater than the paretic (nondominant) soleus MEP_{100} in both fast (p<.01) and slow (p=.01) stroke groups but not controls (p=.54). For the TA muscle, there was also a significant group by limb interaction for the MEP_{100} ($F_{2,40}$ =6.69) (p<.01). Between-group pairwise post hoc comparisons showed that the TA MEP_{100} in the paretic limb was less in the fast-stroke (p=.04) and slow stroke groups (p<.01) than the control group (Figure 2-4). Tibialis anterior MEP_{100} in the paretic limb was not different between the fast versus slow-stroke group (p=.43). Tibialis anterior MEP_{100} in the nonparetic limb showed a similar pattern to the soleus muscle, but was not statistically

different in the slow-stroke group versus the fast-stroke (p=.18) or controls groups (p=.19). Nonparetic TA MEP_{100} was not different between the fast-stroke and the control groups (p=.993) (Figure 2-4). Within group comparisons showed that the nonparetic TA MEP_{100} was greater than the paretic TA MEP_{100} in the slow-stroke (p<.01) and the fast-stroke (p=.03) group but not the control (p=.55) group.

Discussion

This study provides novel evidence that plantarflexor muscles of stroke survivors with poor walking recovery present with greater corticomotor impairments than dorsiflexor muscles during an active motor state. While differences in post-stroke corticomotor symmetry were not observed between dorsiflexors and plantarflexors at rest, greater levels of corticomotor asymmetry between the paretic and nonparetic limb were observed in the plantarflexors muscles during active muscle contraction in stroke survivors with the slowest walking speeds. Further, in addition to reduced paretic corticomotor excitability, greater nonparetic corticomotor excitability was observed in the plantarflexors of stroke participants when compared to neurologically-intact controls. This atypical nonparetic corticomotor excitability was greatest in individuals with poor walking recovery. Together, these findings show that greater neural impairments exist in plantarflexors muscles versus dorsiflexors following stroke, and that corticomotor drive to the nonparetic lower limb is enhanced in stroke survivors

compared to neurologically-intact individuals and is greatest in individuals with poor post-stroke walking recovery.

In general, we observed differences in corticomotor input to paretic and nonparetic limbs in stroke groups when compared to neurologically-intact controls and these differences were greatest in the slow-stroke group and plantarflexor muscles. These findings are consistent with previous upper extremity research showing corticomotor asymmetry is associated with the level of functional motor recovery[23,27,109] and previous biomechanical studies showing that impairment of propulsion is the primary limiter of post-stroke walking function.[71,81,140] Although dorsiflexor corticomotor symmetry improved during the active condition from rest in both fast and slow-stroke groups, we did not observe this modulation of corticomotor symmetry in the soleus muscle (Figure2-2). Interestingly, while there were no differences in corticomotor symmetry between muscles within each group at rest, the slow-stroke group showed differences in corticomotor symmetry between TA and soleus muscles during the active condition. It is possible that during paretic plantarflexion in those participants with poor motor recovery, there was an increase in interhemispheric inhibition from the nonlesioned to the lesioned hemisphere lower extremity primary motor cortical area, as has been reported in the upper extremity during paretic hand contraction in individuals with poor paretic hand function.[24,100] This increased interhemispheric inhibition could have suppressed the typical enhancement of the MEP response in the paretic limb that occurs with muscle

contraction in individuals with poor walking recovery. During nonparetic plantarflexion contraction, interhemispheric disinhibition from the lesioned hemisphere could contribute to increased excitability of the nonlesioned hemisphere and the enhanced MEPs observed in the nonparetic limb when compared to neurologically-intact controls.[22,23,111,141] When looking at differential contributions of the paretic and nonparetic limbs to observed corticomotor symmetry, both the TA and soleus muscles showed similar patterns of suppression of paretic and enhancement of nonparetic limb corticomotor input compared to neurologically-intact controls (Figure2-4). However, the magnitude of difference in each limb during the active condition was greater in the plantarflexors than the dorsiflexors in both fast and slow-stroke groups. The paretic TA was 34% suppressed in fast-stroke and 47% suppressed in slow-stroke, while the soleus MEP amplitude was 40% suppressed in fast-stroke and 59% suppressed in slow-stroke compared to neurologically-intact controls. Additionally, the nonparetic TA MEP amplitude showed no discernable difference in the fast-stroke group and a 23% enhancement in the slow-stroke group, while the soleus MEP amplitude showed a 42% enhancement in the fast-stroke group and an 89% enhancement in the slow-stroke group when compared to neurologically-intact controls during the active condition (see Figure2-4). Thus, it is conceivable that the plantarflexors may be more affected by atypical interhemispheric interactions than dorsiflexors during an active motor state. Consistent with upper extremity research,[24,100] these interhemispheric interactions may show the greatest abnormalities during muscle contraction. Future research utilizing advanced technologies to directly

investigate interhemispheric interactions in lower extremity motor regions during active dorsi- and plantarflexion may shed some light on the underlying cortical neuronal mechanisms that contribute to these cortical behaviors.

This study provides novel evidence that robust changes occur in the nonlesioned hemisphere of stroke survivors that enhance corticomotor drive to the nonparetic lower extremity compared to neurologically-intact controls, and that the degree of nonparetic corticomotor enhancement is associated with level of post-stroke motor impairment. These findings suggest that either 1) the nonlesioned hemisphere may impede walking recovery in individuals with poor post-stroke walking ability or 2) nonlesioned hemisphere over-activity may be a strategy used by the most severely-affected individuals to achieve their current level of post-stroke walking function. Bradnam et al[142] et al posited that, in the upper extremity, the nonlesioned hemisphere likely plays a beneficial role in regaining paretic arm and hand motor function in patients with poor corticospinal tract integrity. In contrast, nonlesioned hemisphere over-activity may interfere with motor recovery in patients with intact corticospinal pathways from the lesioned hemisphere to the paretic upper extremity.[142] This implicates that each of these patient subgroups could benefit from two different rehabilitation approaches. Future research investigating corticomotor input changes to the paretic and nonparetic limb in response to rehabilitation in each of these patient subgroups as they relate to changes in motor function could provide more information regarding the role of the nonlesioned hemisphere in post-stroke walking recovery.

Overall, corticomotor symmetry measures for both the TA and soleus muscle were reduced in the slow-stroke versus the fast-stroke group (Figure2-2), which is consistent with previous research showing relationships between corticomotor symmetry and level of motor function in the upper extremity.[26,143] However, we observed high inter-group variability in corticomotor symmetry measures between the fast and slow-stroke groups in both the dorsiflexor and plantarflexors muscles (see Table 2). The neurophysiologic and neurobiologic factors underlying the type and degree of neuroplasticity underlying cortical imbalance following stroke are unclear. There is evidence that neuroplasticity in the motor cortex is, in part, genetically determined.[144] Interestingly, Di Lazzaro et al[145] recently found that stroke survivors who possessed the genetic Val66Met brain derived neurotrophic factor (BDNF) polymorphism had greater corticomotor symmetry in the paretic and nonparetic hand muscle than those who did not possess the polymorphism. They concluded that impaired secretion of neurotrophin BDNF in individuals with the polymorphism suppressed amplifications of glutamate-dependent plasticity that typically occurs following stroke and likely contributed to corticomotor asymmetry.[145] In the present study, it is possible that a greater number of individuals in the fast-stroke group could have possessed this genetic polymorphism, and could have been more resistant to post-stroke neuroplastic changes leading to hemispheric imbalances, maintaining greater levels of corticomotor symmetry during the chronic stage of post-stroke motor recovery compared to their slow-walking counterparts. Future research could

investigate the role of genetic factors on lower extremity corticomotor asymmetry and post-stroke walking recovery.

Limitations:

Some limitations of the present study are important to consider in the interpretation of our results. The small sample size and heterogeneity of individuals in the stroke groups limit generalizations to the general stroke patient population. In the present study, we compared stroke groups to a younger neurologically-intact control group that were not age-matched. Previously, MEP amplitudes were found to be lesser in older versus younger adults.[146] Thus, the present control group provided a more conservative between-group comparison of nonparetic MEP amplitudes and would not have affected the corticomotor symmetry comparisons. It is possible that more robust differences in nonparetic MEP amplitude and lesser differences in paretic MEP amplitude between groups could have been observed for each muscle when compared to an age-matched control group. Because all participants with stroke in the present study were able to walk without the assistance of another person, it is difficult to generalize results to non-ambulatory stroke survivors. Individuals were not stratified for lesion size and location, which could have influenced corticospinal tract integrity and paretic limb MEP amplitude values. In this study, we did not observe differences in normalized pre-stimulus EMG activity levels in the nonparetic limb for either muscle between groups. However, we observed that severely affected participants with stroke had difficulty modulating paretic limb activation levels and were

contracting both the TA and soleus muscles at a greater comparable effort than neurologically-intact controls (See Appendix A, Figure A.2.1.). This could have overestimated the already reduced paretic MEP amplitude measures of the slow-group and should be considered when interpreting differences in magnitude of paretic limb corticomotor excitability between groups.

Conclusions

This is the first study to provide neurophysiologic evidence that post-stroke corticomotor drive to plantarflexors during an active motor state is impaired to a greater degree than that of dorsiflexors and that these impairments are associated with walking function in individuals with chronic stroke. These findings support biomechanical evidence that targeting plantarflexor motor function in rehabilitation could be critical to maximize post-stroke walking ability. Abnormally greater corticomotor excitability in the nonparetic soleus in individuals with poor walking recovery indicates that neural function of the nonparetic limb plays a role in walking recovery following stroke. Rehabilitation strategies including the nonparetic lower limb could further benefit functional walking outcomes in stroke survivors. Future work could investigate the effects of rehabilitation strategies in restoring corticomotor symmetry between paretic and nonparetic limbs on changes in walking function.

Table 2-1. Participant characteristics. Mean values±1SD are shown. FMA: Fugl-Meyer Assessment.

	Fast-stroke	Slow-stroke	Controls
N	16	13	14
Age (yrs)	60 ± 10	62 ± 12	22 ± 2
Sex (male)	9	10	6
Time since stroke (mo.)	50 ± 35	56 ± 86	N/A
Gait speed (m/s)	0.98 ± 0.19	0.43 ± .019	N/A
FMA Lower Extremity	26 ± 5	18 ± 5	N/A

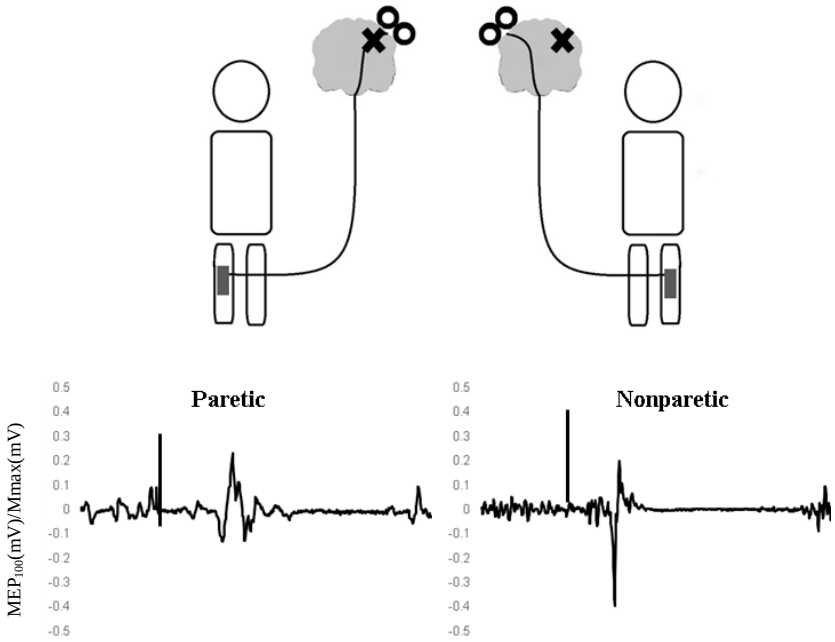

Figure 2-1. Schematic of the TMS testing paradigm for the paretic and nonparetic lower extremities (top). Representative example of MEP_{100}s from the paretic (bottom left) and nonparetic (bottom right) soleus muscles in one participant with stroke during active plantarflexion.

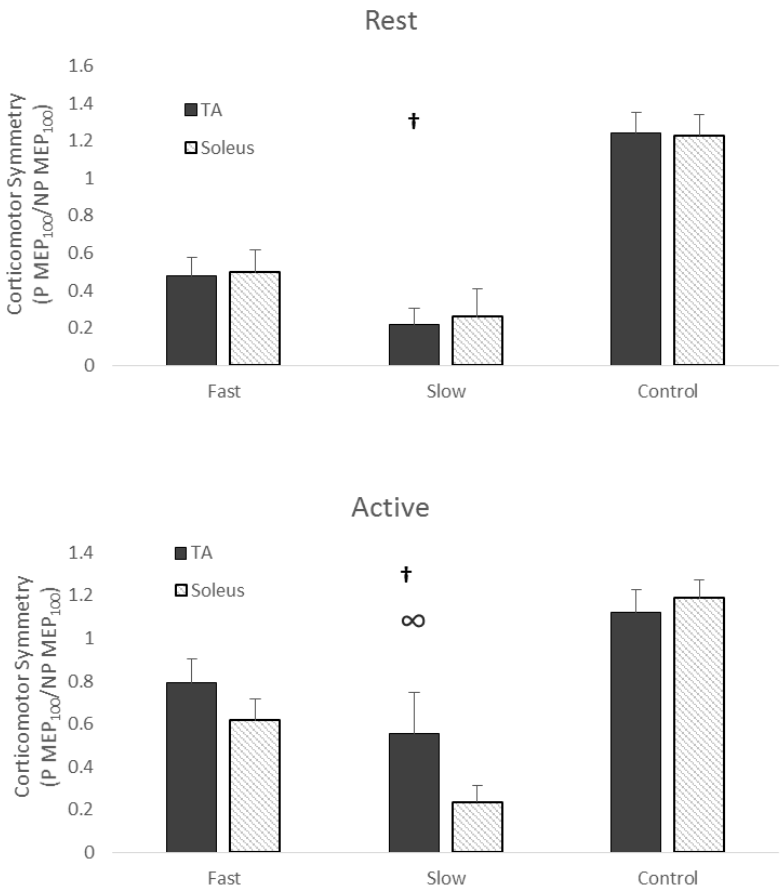

Figure 2-2. Corticomotor symmetry values (mean ±1SE) for the TA and soleus muscles presented for each group during the rest (top) and active condition (bottom). Main effects of group ($F_{2,39}$ =29.13) ($p<.01$) but not muscle ($F_{1,39}$ =0.04) ($p=.835$) were observed during the resting condition. Main effects of muscle ($F_{1,40}$ =4.14) ($p=.04$) and group ($F_{2,40}$ =14.23) ($p<.01$) were observed during the active condition (bottom). † Indicates main effect of group (see results for post-hoc comparisons). ∞ Indicates main effect of muscle. P: paretic; NP: nonparetic; TA: tibialis anterior muscle.

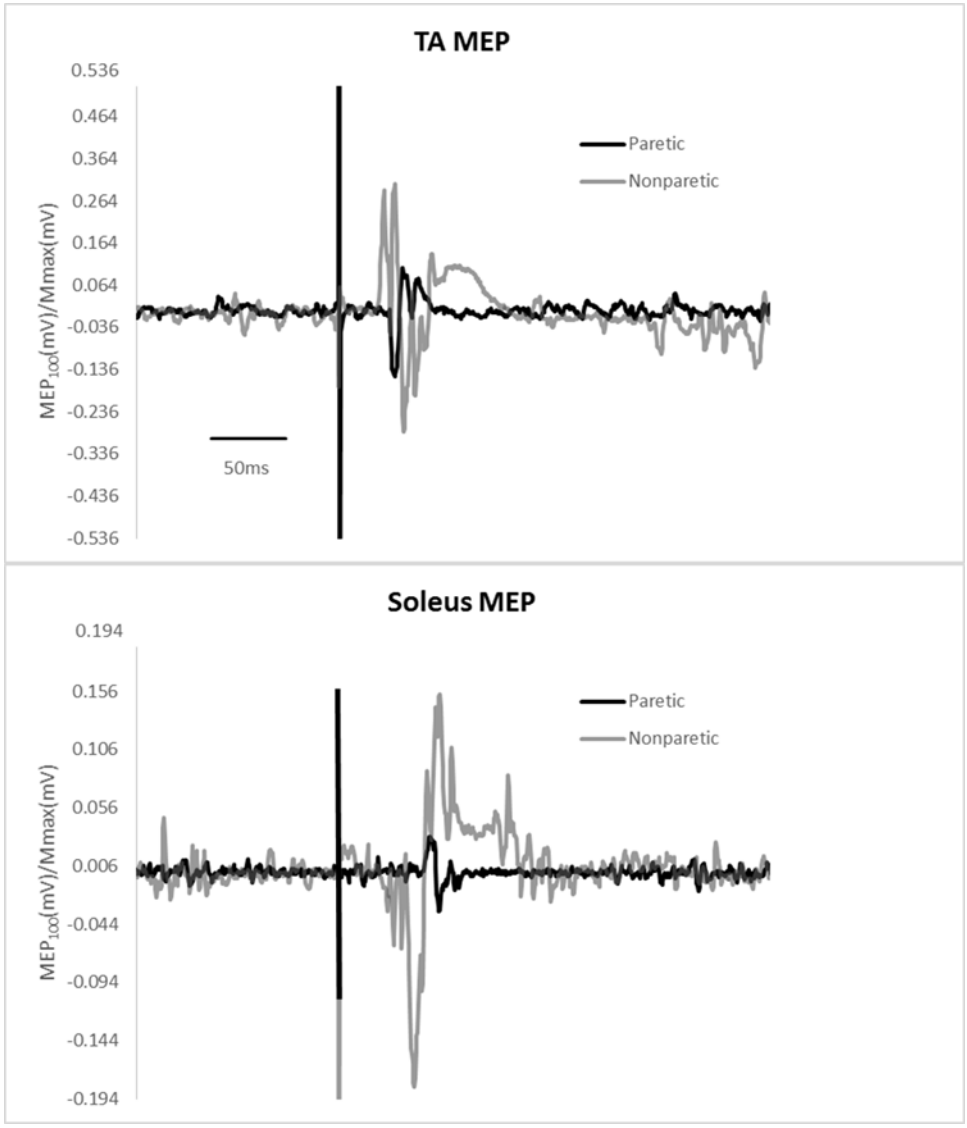

Figure 2-3. Representative raw MEP_{100} data from the paretic and nonparetic TA (top) and soleus (bottom) muscles of a participant in the slow-stroke group during the active condition. Note that the y-axis for each muscle has been scaled to ± mean neurologically-intact MEP_{100} values for the TA (0.536) and soleus (0.194) muscles, respectively.

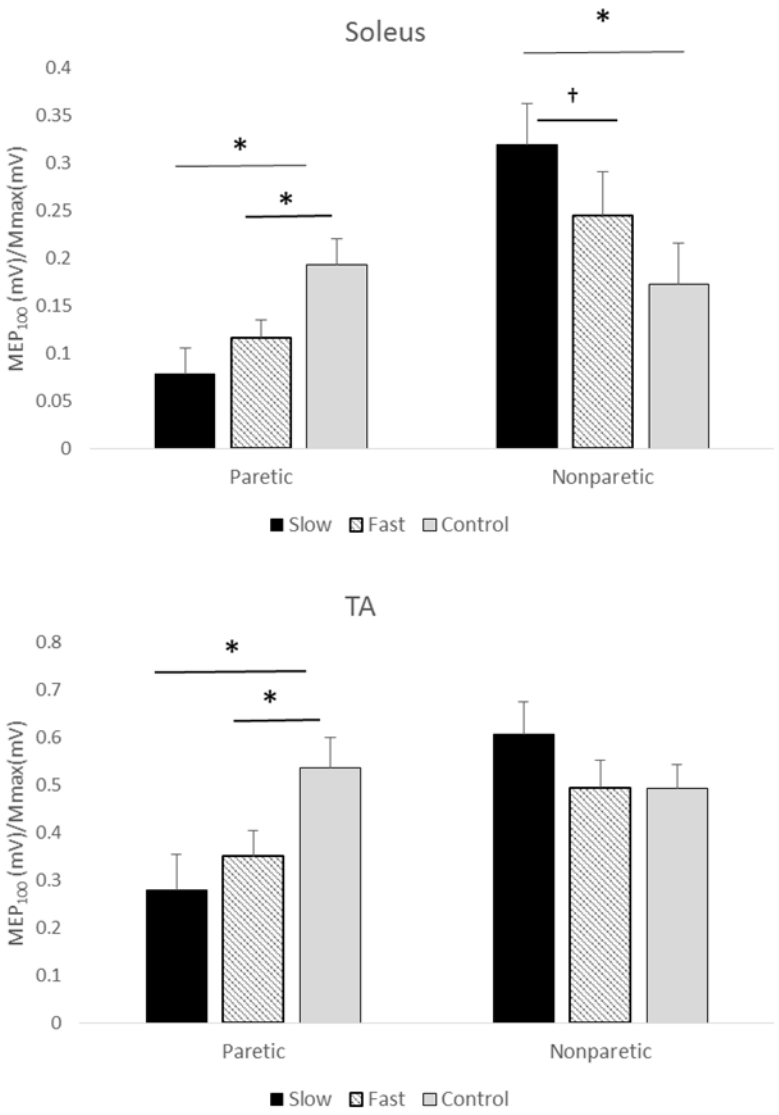

Figure 2-4. MEP amplitude values (mean±1SE) for TA (top) and soleus (bottom) muscles for each group during the active condition. There was a significant group by limb interaction for both the TA ($F_{2,40}$ *=6.69) (*$p<.01$*) (top) and the soleus (*$F_{2,40}=15.64$*) (*$p<.01$*) (bottom). Between-group differences for the paretic and nonparetic limbs are shown. *Indicates significance at the* $p<.05$ *level. †Indicates trend with* $p=.11$*.*

Chapter 3

ATYICAL CORTICAL DRIVE DURING ACTIVATION OF THE PARETIC AND NONPARETIC LOWER EXTREMITY MUSCLES IS RELATED TO WALKING FUNCTION IN CHRONIC STROKE

Abstract

Objective: Nonparetic limb muscle activation can affect motor control and performance of the paretic limb of stroke survivors with poor motor recovery. The neural mechanisms underlying the influence of the nonparetic limb on paretic limb motor function remain ambiguous. The purpose of this study was to compare corticomotor drive to the paretic limb during paretic muscle activation, nonparetic muscle activation, and resting conditions in stroke survivors with poor versus good walking recovery.

Methods: Eighteen individuals with stroke were dichotomized into fast or slow walking groups. Transcranial magnetic stimulation (TMS) was used to collect motor evoked potentials (MEPs) from the tibialis anterior of each lower extremity during rest, paretic muscle contractions, and nonparetic muscle contractions. The average MEP of the paretic leg during TMS at maximal intensity (MEP_{100}) for each condition was compared within and between groups.

Results: Slow-walkers showed greater MEP responses during the nonparetic contraction than during the paretic contraction or rest conditions. In contrast, fast-walkers had greatest MEP responses during the paretic contraction.

Conclusions: Alterations in corticomotor excitability of the paretic dorsiflexors occur during nonparetic muscle activation in stroke survivors with poor walking recovery. **Significance:** Understanding neural mechanisms underlying post-stroke walking ability can help to identify specific patient deficits that may limit function.

Introduction

Following a neurological injury, recovery of lower extremity control and the ability to walk is a primary goal of stroke patients.[2] However, many individuals are left with long term disability of functional ambulation following stroke, despite current standard rehabilitation.[2] Gains in neuroscience research over the last several decades have enhanced our understanding of structural changes in the brain that may underlie functional disability following stroke.[3] Studies have demonstrated the "adaptive capacity" of the central nervous system and the striking ability of neurons to modify structure and function in response to environmental stimuli.[3,101,147] However, there remains a large gap in our current understanding of this neuroplasticity and neurophysiologic mechanisms that affect functional recovery in humans post-stroke. Indeed, this lack of understanding has limited our ability to develop effective neurorehabilitation treatments for recovery of motor function.[3,99]

Over the past decade, studies using transcranial magnetic stimulation (TMS) to investigate changes in corticomotor excitability following stroke have offered valuable insight into mechanisms for functional recovery of the upper extremity.[99] Research has found long-term mechanisms of repair and recovery in the brain are associated with varying degrees of functional motor recovery.[19,99] Following stroke, TMS measures of decreased corticomotor excitability in the paretic upper extremity during stimulation of the *lesioned (contralateral)* hemisphere are associated with poor motor recovery[20,21,30] and increased excitability is associated with good functional

recovery.[17,19,30] Conversely, paretic motor responses during stimulation of the *nonlesioned (ipsilateral)* hemisphere are related to poor recovery.[24,25] These results have created a neurophysiologic model of decreased excitability and increased inhibition of the lesioned hemisphere coupled with over-activity and disinhibition of the nonlesioned hemisphere in those with poor upper extremity recovery.[20,25,30] The relationship of this atypical cortical balance can be quantified[148,149] and has been shown to behave differently during motor function than during rest in stroke.[24] Studies utilizing new rehabilitation techniques for the upper extremity taking advantage of these mechanisms of cortical neuroplasticity have enabled individuals to reach new gains in functional recovery beyond those made with standard rehabilitation.[150,151]

Despite our growing knowledge of changes in cortical remodeling that occurs for the upper extremity, our understanding of these functional recovery mechanisms in the lower extremity is limited. New technologies in TMS have helped to overcome previous limitations in our ability to target muscle representations of the lower extremity that are located more deeply within the primary motor cortex.[152] Although there are differences between the upper and lower extremity motor organization and control such as anatomical locations of motor maps and lack of fine motor task performance, it is well-established that the motor cortex is actively and intricately involved in lower extremity function such as ambulation.[153] Evolving research has indicated that cortical remodeling could behave in a similar pattern to that of the upper extremity, with increased excitability to the paretic leg from the lesioned hemisphere being related to good functional recovery of independent transfers[39] walking and stair

climbing.[40] There is little evidence on the role of hemispheric balance in lower extremity functional recovery. Madhavan et al.[16] found stronger conductivity from the nonlesioned hemisphere to the paretic ankle muscles was related to poor performance accuracy during an anti-phasic ankle tracking task. Still, other studies have found that ipsilateral projections from the nonlesioned hemisphere are essential to functional motor recovery of behaviors involving less cortical input.[37,38] Lack of research combined with our inability to reconcile the basis for conflicting results of these studies has limited our understanding of the possible mechanisms underlying motor recovery of functional behaviors such as ambulation, which involve less cortical input than upper extremity behaviors such as reaching and grasping.[153]

Another factor that has been shown to influence motor performance of paretic extremities post-stroke is in-phase activation of homologous muscles of the nonparetic contralateral extremity. Greater performance in paretic arm movements have been observed when they are performed in-phase simultaneously with the nonparetic arm than when they are performed with the paretic arm in isolation.[43-45] Additionally, individuals post-stroke often demonstrate involuntary symmetric movements of the paretic limb during effortful nonparetic limb movement.[41,42] Likewise in the lower extremity, paretic motor performance improves during bilateral in-phasic tasks.[46,47] Tseng and Morton[48] demonstrated that muscle activation patterns in the paretic dorsi- and plantarflexors that were related to kinematic performance showed the greatest abnormalities during anti-phasic bilateral ankle motor tasks.[48] Together, these findings suggest that muscle activation of the nonparetic limb affects the motor behavior of the

paretic limb, likely through corticospinal system projections.[48] If such corticospinal projections were active during gait, a motor behavior requiring anti-phasic bilateral lower extremity motor coordination, then this could contribute to functional walking deficits in individuals post-stroke. However, no studies to date have directly investigated the differential effect of muscle activation within the paretic and nonparetic limbs on corticomotor input to the lower extremity.

Mechanisms responsible for functional recovery of the lower extremity in stroke are unclear, therefore limiting the ability of rehabilitation specialists to target deficits impairing lower extremity function such as gait. An understanding of cortical substrates that underlie recovery of motor behaviors during differential activation of the paretic and nonparetic limb involved in walking may explain why some patients respond well to rehabilitation interventions such as gait training while others may never regain adequate motor function for safe community ambulation.[132] The purpose of this study was to investigate the differences in corticomotor excitability of the paretic limb during resting and active conditions of the paretic and nonparetic dorsiflexors muscles.

Methods

A cross-sectional design was used. Independent variables were group (fast-walkers or slow-walkers) and condition of contraction (paretic, nonparetic, rest). The dependent variable was mean peak-to-peak MEP amplitude at 100% stimulator

intensity (MEP_{100}) measured with TMS. The study population included 18 individuals (13 males, mean age 61.3±8.3 years, mean time since stroke 57±65 mo.) with chronic stroke (>6 mo.) recruited from local physical therapy clinics and senior centers (Table 3-1). These values represent mean and standard deviation. The experimental protocol was approved by the University of Delaware IRB and all participants gave written informed consent. All participants sustained a single cortical or subcortical stroke and were able to walk a distance of >10 meters without assistance of another person. Exclusion criteria included more than one previous stroke, cerebellar involvement, pain in the lower extremities at rest or during walking, presence of any neurologic conditions other than stroke, and any unsafe TMS testing criteria.[154] Participants performed a 10-meter walk test to quantify self-selected walking speeds.[132] As previous research has established a self-selected walking speed 0.8 m/s is necessary for unrestricted community ambulation in the stroke patient population,[132] participants were dichotomized into a slow-walking (<0.8m/s) and fast-walking group (>0.8m/s).

Assessment of Cortical Excitability

Participants donned an elastic cap and were comfortably seated upright in an arm chair with knee and ankle angles positioned at 90 degrees with both feet resting on the floor for testing. Double differential surface electrodes with integrated ground (BL-AE, B&L Engineering, Santa Ana, CA) were positioned and secured to the skin over the tibialis anterior (TA) muscles bilaterally. EMG activity was recorded bilaterally and simultaneously using a 6 channel active EMG system (BL-EMG-6, B&L Engineering, Santa Ana, CA) and sampled at a rate of 2000Hz with a 330 gain

set on a 16 bit data acquisition board (National Instruments NI USB-6341). The experimenter identified the vertex of the skull and began with the midpoint of the coil aligned antero-posteriorly to the vertex and the coil positioned at the midline of the vertex and 1cm anterior to the frontal midline.[135] Custom LabVIEW software (National Instruments, Austin, TX) was developed and used to set intensities, trigger the TMS pulses, and collect EMG data.

Participants were asked to dorsiflex and maintain a light contraction at 15% of their maximal EMG activity during stimulation while searching for the optimal location for eliciting a MEP of maximal peak-to-peak amplitude.[137] Magnetic pulses were delivered with a magnetic stimulator (Magstim 200, MagStim Ltd, Wales, UK) through a batwing coil (each wing 11cm in diameter) beginning at 10% stimulator output intensity and gradually increasing to the intensity where a MEP was visibly observed on real-time EMG in the TA of the targeted muscle.[137] The coil was moved over the scalp as magnetic stimuli of suprathreshold intensity were delivered and the optimal location for eliciting a MEP of maximal peak-to-peak amplitude was found. Optimal locations for both the paretic and nonparetic TAs during facilitation were consistently found to be located on the contralateral side of the vertex of the targeted muscle in all participants *during contraction of the targeted muscle*. The coil positions were carefully marked on the head and used for all recordings. TMS pulses were applied at a rate of 0.2 Hz ranging from subthreshold through 100% stimulator output at intervals of 3 percent of the stimulator's output. Three pulses at each intensity were delivered in random order to the optimal location.[137] Approximately 60 MEPs were

collected for each trial. Three conditions were tested: resting, paretic TA contraction, and nonparetic TA contraction. During the first trial for each leg, participants were asked to keep both legs completely relaxed for the resting condition. For the paretic contraction and nonparetic contraction conditions participants were asked to dorsiflex only the leg being targeted to 15% of their maximum EMG activity throughout the trial, while keeping the other leg relaxed. The order of the testing leg was randomized. Real-time EMG biofeedback was provided to assist participants in maintaining a constant level of muscle activity. If participants were unable to produce a voluntary motor contraction of the paretic TA, they were asked to maintain an effort that produced an observable increase in EMG that they could maintain. All participants were able to produce an observable increase in volitional EMG for both paretic and nonparetic legs. During post-processing, we quantified the pre-stimulus EMG activity for all conditions to determine that all conditions were met. The root-mean squared of the pre-stimulus EMG of the paretic TA for each condition was calculated during a 100ms window immediately prior to the stimulus artifact for each MEP. EMG was recorded bilaterally and simultaneously during all testing conditions. Testing procedures were repeated twice for each condition and for each leg.

The maximal response to peripheral nerve stimulation (M_{max}) was collected and used for normalization of MEP amplitude for all data. The common peroneal nerve was located through palpation and confirmed with muscle response of the TA to peripheral nerve stimulation at the level of the fibular head. Nerve stimulation was delivered using a custom electrical stimulator (U-DEL, Newark, DE) while subjects

remained seated comfortably in a chair and were asked to relax, with relaxation confirmed with EMG observation. Stimulation was delivered to the nerve with a custom UDEL stimulator using 1ms square electrical pulses of gradually increasing intensities, with 10 seconds between each pulse. The stimulus intensity was increased until no increase in the M-wave was observed with increasing intensity for the TA muscle.

Data Reduction and Analysis:

Resting condition trials were discarded from analysis if the paretic TA and/or nonparetic TA pre-stimulus EMG activity a showed a change in EMG activity from baseline, as determined by the experimenter, and/or was greater than 10μV. Paretic contraction condition trials were discarded from analysis if the EMG activity of the paretic TA was not at least 2.5 standard deviations greater than the resting condition and/or EMG activity in the nonparetic TA was greater than that allowed during the resting condition (10μV). The same procedure was followed for the nonparetic contraction condition for both muscles. Additional trials were collected in individuals who did not meet these criteria for pre-stimulus EMG.

Peak-to-peak amplitudes of MEPs were calculated and normalized to the maximum M-wave. MEP_{100}s were calculated to determine the corticomotor excitability of the paretic leg across conditions, and changes in corticomotor excitability were compared between groups. The average peak-to-peak MEP amplitudes of the paretic TA at 100% stimulator output intensity (MEP_{100}) during the two trials was calculated for each condition (paretic TA contracted, nonparetic TA

contracted, and resting).[29,155] During pilot testing, we quantitatively determined the reliability of stimulus-response curve parameters and average MEP_{100} measures by calculating intraclass correlation coefficients [ICC 3, *k*]. SPSS statistical software was used to perform all analysis.

Results

Optimal coil positions were found at 2.0±0.6 cm lateral and 2.2±0.7 cm anterior for the paretic leg and 2.2±0.5 cm lateral and 2.3±0.6 cm anterior for the nonparetic leg. There was no difference between coil position between subject groups for the paretic leg (anterior, $p = .79$; lateral, $p = .84$) and the nonparetic leg (anterior, $p = .71$; lateral, $p = .86$). The average MEP_{100} within the session showed good reliability within individuals ($ICC_{3, k} = 0.962$) and could be acquired for all participants (see Appendix B, Table B-1). Pre-stimulus EMG activity in the paretic TA during the paretic contraction condition was at least 2.5 standard deviations greater than that of the resting condition for both groups. Appropriate EMG activity levels within the paretic leg for each condition were met by all participants in the fast (paretic contraction = 28.54 ± 20.02μV, nonparetic contraction = 6.36 ± 5.16μV, resting = 6.94 ± 5.81 μV) and slow (paretic contraction = 16.22 ± 9.73μV, nonparetic contraction = 5.54 ± 2.01μV, resting = 4.37 ± 1.77μV) groups. Pre-stimulus EMG activity in the nonparetic TA during the nonparetic contraction condition was also greater than that of the resting condition by at least 2.5 standard deviations for both the

fast (25.01 ± 10.91μV) and slow (17.55 ± 6.84μV) groups. Pre-stimulus EMG activity data are presented in Appendix A (A-2).

All MEP_{100} data met the assumptions of normality, sphericity, and heteroscedasticity. A 2x3 mixed design analysis of variance was used to test if groups (fast or slow walkers) differed between conditions (resting, paretic contraction, nonparetic contraction) for the TA $MEP_{100.}$ There was a significant group by condition interaction for paretic TA MEP_{100} ($F_{2,32} = 10.53$) ($p < .01$) (Figure 3-3). Post-hoc pairwise comparisons were performed using a Bonferroni method. For fast walkers, paretic TA MEP_{100}s during the paretic contraction (0.418 ± 0.242) were significantly higher than resting (.223 ± .251) ($p < .01$) and nonparetic contraction conditions (0.292 ± 0.258) ($p < .01$) (Figure 3-3). There was no difference between paretic TA MEP_{100} during the resting and the nonparetic contraction condition ($p = .157$). A different pattern was observed for slow walkers. There was no difference between paretic TA MEP_{100} during the paretic contraction (0.140 ± 0.170) and the resting condition (0.134 ± 0.189) ($p = .873$). Slow walkers had significantly greater paretic TA MEP_{100}s between nonparetic (0.274 ± 0.244) versus paretic ($p < .01$) contraction. They also had significantly greater paretic TA MEP_{100}s during the nonparetic contraction than the resting condition ($p = .01$) (Figure 3-3). Examples of raw paretic MEP data from a fast and slow walker are presented in Figure 3-2. Patterns in changes in paretic TA MEP_{100} between paretic and nonparetic contraction conditions were different between fast vs. slow walkers; all fast walkers showed an increase in paretic TA MEP_{100} from nonparetic contraction during paretic contraction while all slow

walkers showed a decrease in paretic TA MEP_{100} from nonparetic contraction during paretic contraction (Figure 3-4).

Discussion

The current study provides novel evidence about the neural origins of the interference that nonparetic muscle activation has on paretic motor function in stroke survivors. We observed substantial differences between individuals with good versus poor walking recovery in corticomotor response under each condition of muscle contraction. These observed differences showed that stroke survivors with poor walking recovery rely on activation of the nonlesioned hemisphere and contraction of the nonparetic leg to achieve corticomotor drive to the paretic leg, which is different from corticomotor responses observed in stroke survivors with good walking recovery.

We observed that corticomotor excitability of the paretic leg in the slow group was *greatest* during the *nonparetic* TA contraction and that the fast group showed *greatest* excitability during the *paretic* TA contraction. These results demonstrate that changes in corticomotor drive to the lower extremity during the nonparetic TA contraction are different between individuals of high and low-level functional recovery. Our results may support previous findings using neuroimaging methods that deficient corticomotor conductivity to the paretic leg from the lesioned hemisphere, and stronger conductivity from the nonlesioned hemisphere to the paretic leg impede paretic leg motor performance.[16] We posit that increased corticomotor excitability to

the paretic leg observed during nonparetic limb activation in the present study could potentially be due to greater ipsilateral cortical projections from the nonlesioned hemisphere that become activated during nonparetic dorsiflexion contraction in individuals with poor lower extremity recovery. This explanation is in agreement with the upper extremity model of poor motor recovery post-stroke [25,29,30,149] and may provide a neurophysiologic explanation for observations of involuntary activation of the paretic limb during homologous nonparetic limb muscle activation.[44-46,48] Inappropriate corticomotor facilitation tied to activation of the nonparetic limb could affect functional use of the lower extremities and may underlie gait impairments resulting in slow walking speeds.

Interestingly, findings indicate that contraction of the paretic leg failed to facilitate corticomotor drive in slow walking subjects. In the upper extremity, activation of paretic hand muscles increased transcallosal inhibition of the nonlesioned hemisphere to the lesioned hemisphere in individuals with chronic stroke.[24] It is possible that the lower extremity in individuals with poor recovery behaves similarly to that of the upper extremity;[24,149] during activation of the paretic TA, transcallosal inhibition from the nonlesioned hemisphere may have increased, resulting in suppression of the MEP response between the resting and paretic contraction conditions. Altered interhemispheric interactions may also explain why we did not observe a greater muscle response during rest or paretic muscle contraction conditions in the slow walking group, despite searching for the optimal location for stimulation of the paretic TA on either side of the vertex. Two explanations of these results may be

possible: 1) during activation of the nonparetic TA transcallosal inhibition from the nonlesioned to the lesioned hemisphere decreased,[24] which, despite targeting of the nonparetic TA through the nonlesioned hemisphere, allowed for the magnetic stimulation current at high intensities to reach the lesioned hemisphere and facilitate MEP responses in the paretic leg or 2) ipsilateral projections from the nonlesioned hemisphere may become more active during nonparetic dorsiflexion contraction, facilitating MEP responses within the paretic TA in individuals with poor lower extremity recovery.[25,29,149]

In the presence of lost function following brain injury, one of the most common and consistent observations is that individuals develop compensatory strategies to perform daily activities.[3,29] Those individuals most involved may have shown decreased reliance on the paretic limb and increased reliance on the nonparetic limb, which has been shown to be related to major neuronal reconstruction and reorganization in the lesioned and nonlesioned hemispheres following unilateral cerebral injury.[101] Even in neurologically-intact individuals, coupling immobilization and non-use of one extremity with heavy reliance on the contralateral extremity for functional tasks will result in hemispheric imbalances of cortical excitation and inhibition.[83] Results of the present study support the hypothesis that slow-walkers could undergo neuronal changes that result in the impaired ability to differentially activate the paretic and nonparetic dorsiflexor muscles through similar mechanisms. Previously, TMS measures of the TA obtained during voluntary dorsiflexion were found to be similar to those obtained during the swing phase of walking in able-bodied

adults.[6] If such atypical cortical responses observed during activation of the nonparetic TA in the present study continued during ambulation, this could contribute to atypical interlimb relations and altered kinetics and kinematics leading to dysfunctional gait and slowed walking speed.[156] If slow walkers were able to improve cortical responses to the paretic TA, these changes in corticomotor behaviors could possibly translate to improvements in lower extremity function for these individuals.

Limitations

Due to the cross-sectional design of the present study, it cannot be determined if observed cortical differences between the fast and slow walking groups existed prior to recovery of ambulation or if differences in functional recovery of walking contributed to different neurophysiologic mechanisms of cortical plasticity. Because of the anatomy of lower extremity muscle representation within the motor cortex, it is improbable that one hemisphere can be stimulated in isolation, particularly at high stimulator output intensities. Thus, it is not possible to tell if MEP responses within the paretic leg are a consequence of increased corticomotor pathway strength from the lesioned or the nonlesioned motor cortex. Although the "hotspot" locations for each muscle were consistently found to be on the contralateral hemisphere, slight variability in coil placement between the two hemispheres could have influenced the magnitude of corticomotor excitability differences between limbs within a subject and magnitude of corticomotor excitability between subjects. For example, if coil placement of the nonparetic TA hotspot on the nonlesioned hemisphere was closer to the vertex, then this could more easily induce MEPs within the paretic TA through stimulation of the

lesioned hemisphere, creating greater corticomotor excitability than if the coil were positioned more lateral to the vertex. Future studies using neuroimaging techniques could distinguish spatial locations within the cortex that are active during nonparetic limb contraction and greatly help in the interpretation of these results. Participants who were unable to produce visible voluntary muscle contractions were contracting their TA muscles at a higher volitional effort to other participants (i.e. 15%), which may have influenced the results (see Appendix A, A3.1 for full description). It should be acknowledged that other factors independent of stroke that were not measured in the present study can affect gait speed and corticomotor excitability such as white matter hyperintensities and cerebral perfusion.[157,158] Relatively small sample sizes used in the present study require caution when generalizing to larger post-stroke populations. Finally, it should be noted there was a large difference in the walking speeds between groups, with no participants within the middle range of gait speeds represented in this study. Future research is needed to investigate the cortical behaviors of individuals in this middle speed range.

Conclusions

The findings of this study show that, similar to the upper-extremity, the normal balance of cortical excitability to the lower extremity is altered in the most affected individuals post-stroke. This atypical corticomotor drive is likely dependent on activation of the nonlesioned hemisphere during volitional contraction of the

nonparetic leg. This may suggest that improvements in atypical cortical drive may lead to improved gait speeds. Novel rehabilitation strategies that have been shown to enhance corticomotor input from the lesioned hemisphere, decrease corticomotor input from the nonlesioned hemisphere and improve hemispheric imbalance to limbs in the upper extremity, such as constraint induced movement therapy[59] and functional electrical stimulation,[62,63] could potentially improve lower extremity motor function through similar mechanisms. Future research investigating the effectiveness of such rehabilitation strategies in promoting positive changes in patterns of corticomotor excitability within the lower extremity could empower clinicians to implement therapies that target individual deficits and ultimately lead to improvements in functional ambulation.

Table 3-1. Subject (N=18) characteristics and TMS results for the tibialis anterior muscle [115] doi: 10.1016/j.clinph.2015.06.013.

Subj	Age (yrs)	Stroke Etiology	**Time Since Stroke (mo.)**	**P Side**	**Gait Speed (m/s)**	**Paretic TA MEP_{100} (avg.) (/Mmax)**		
						NP Contr.	*P Contr.*	*Rest*
S155	54.2	ischemic	96	L	1.16	0.52	0.655	0.570
S368	70.7	hemorrhagic	20	L	1.44	0.208	0.549	0.397
S400	78.0	ischemic	102	L	0.94	0.367	0.388	0.287
S014	63.5	ischemic	95	R	1.92	0.070	0.256	0.111
S436	61.5	ischemic	83	R	1.01	0.855	0.939	0.851
S432	54.0	ischemic	18	L	1.13	0.199	0.226	0.092
S407	61.5	ischemic	20	L	1.13	0.323	0.342	0.211
S071	47.6	ischemic	45	L	0.84	0.015	0.262	0.092
S546	55.0	ischemic	17	R	0.90	0.018	0.119	0.013
S549	62.0	ischemic	51	L	1.00	0.358	0.447	0.102
S369	59.1	ischemic	12	L	0.18	0.039	0.011	0.019
S383	48.7	ischemic	84	R	0.26	0.411	0.277	0.187
S313	62.4	ischemic	62	R	0.32	0.723	0.501	0.583
S037	65.4	ischemic	274	L	0.32	0.071	0.053	0.053
S287	63.4	ischemic	9	L	0.09	0.129	0.102	0.003
S294	55.1	ischemic	12	R	0.45	0.16	0.032	0.038
S575	77.0	ischemic	7	L	0.40	0.158	0.016	0.027
S006	65.0	ischemic	17	L	0.43	0.503	0.126	0.068

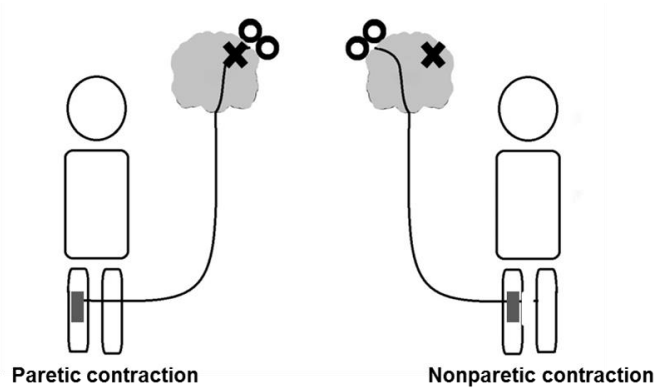

Figure 3-1. Schematic of the TMS testing paradigm and coil locations during the paretic and nonparetic contraction conditions. During the paretic contraction condition, the coil was positioned at the paretic TA hotspot. During the nonparetic contraction condition, the coil was positioned at the nonparetic TA hotspot.

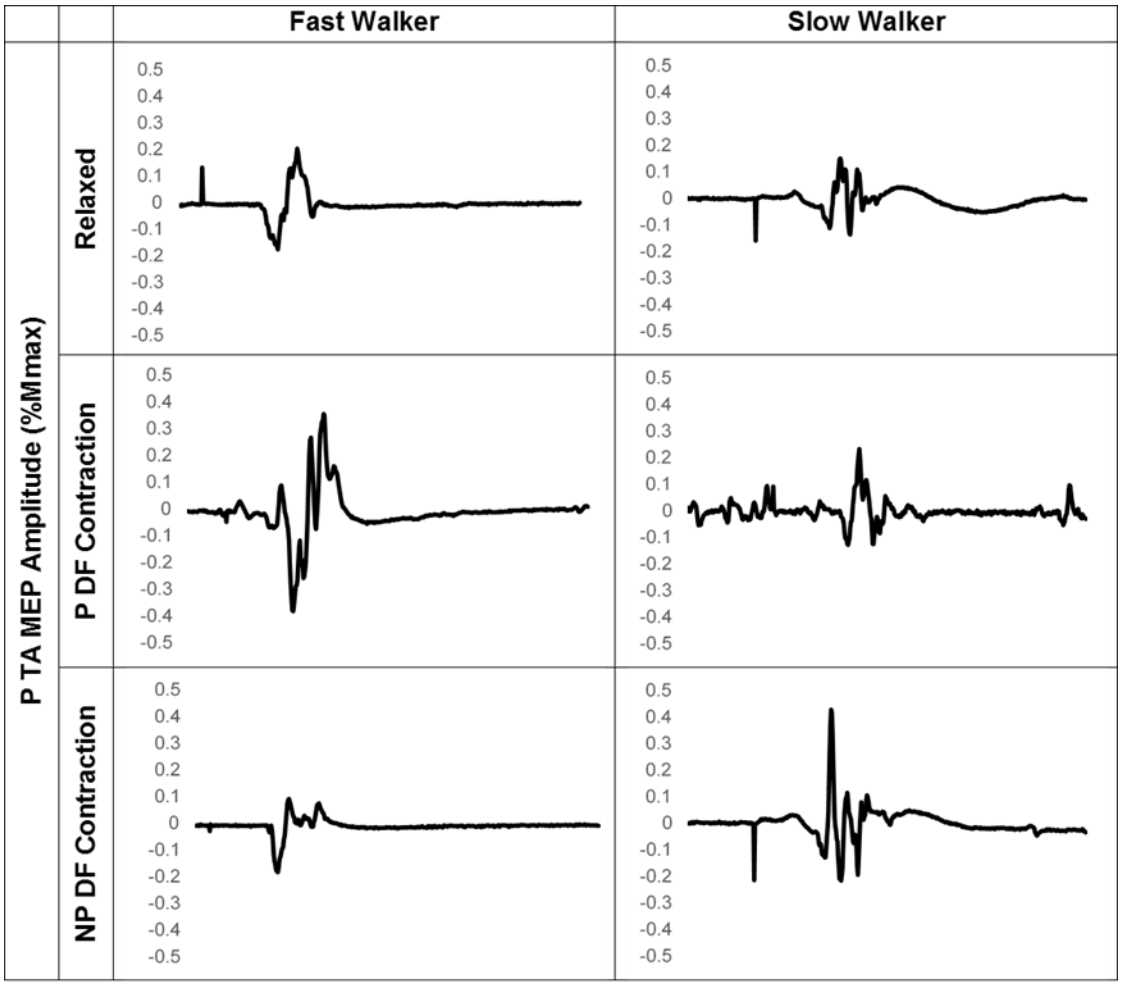

Figure 3-2. Example raw paretic TA MEP_{100} data from a subject in the fast group (left) and a subject in the slow group (right) is shown for the resting (fast: 0.380, slow: 0.287), paretic contraction (fast: 0.738 slow:0.361), nonparetic contraction (fast: 0.273, slow: 0.630). The main effects of group and condition were also significant. TA MEP_{100} was significantly greater in the fast walkers ($F = 20.52$, $p < .01$) compared to the slow walkers ($F = 5.41$, $p = .02$). Between-group pairwise comparisons revealed that MEP_{100} during the paretic contraction was different between groups ($F_{1,16} = 7.53$, $p = .01$). There was no difference in MEP_{100} between groups for the resting ($F_{1,16} = 0.69$, $p = .417$) or nonparetic contraction condition ($F_{1,16} = 0.02$, $p = .878$). [115] *doi: 10.1016/j.clinph.2015.06.013.*

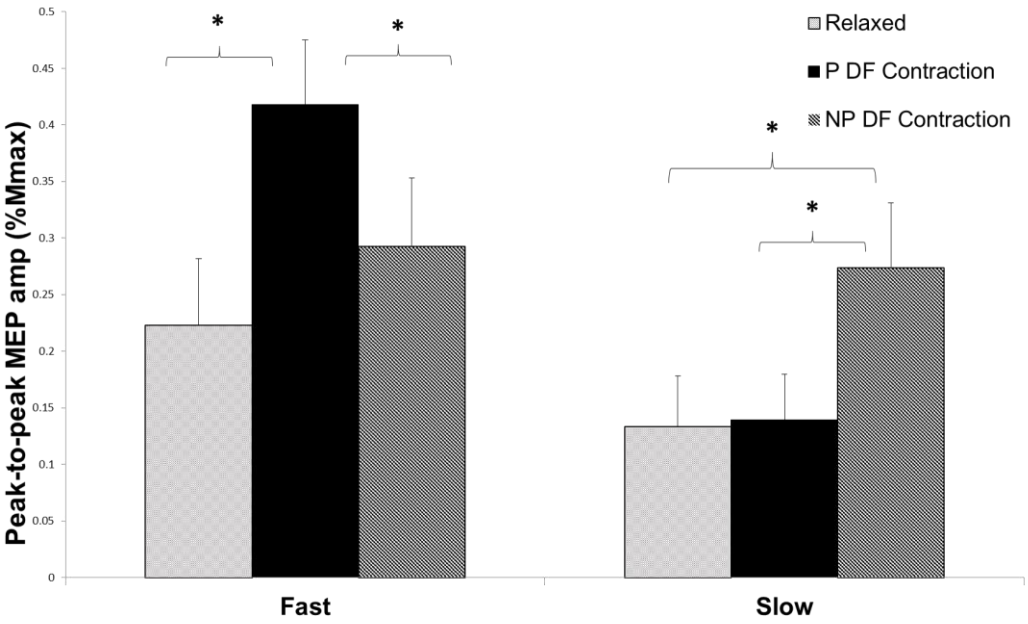

Figure 3-3. Paretic TA MEP_{100} (mean±SE) during each condition. Presented are the mean and standard errors for each condition. Differences were observed in the slow group between TA MEP_{100} during the nonparetic contraction and paretic contraction condition as well as the resting condition. Differences were observed in the fast group between TA MEP_{100} during the paretic contraction and the nonparetic contraction condition as well as the resting condition. A significant difference in paretic TA MEP_{100} is signified by asterisks (*) at $p \leq .01$. [115] *doi: 10.1016/j.clinph.2015.06.013.*

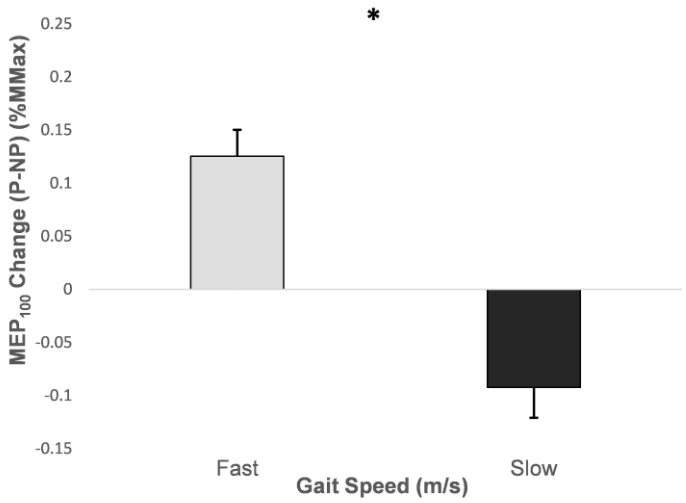

Figure 3-4. Changes in P TA MEP_{100} (mean±SE) between paretic and nonparetic contraction conditions for the fast vs. slow walkers. Presented are the mean and standard errors for each group. A significant difference for change in TA MEP_{100} between fast versus slow walkers is signified by asterisks (*) at $p < .01$. [115] *doi: 10.1016/j.clinph.2015.06.013.*

Chapter 4

SYMMETRY OF CORTICOMOTOR INPUT TO PLANTARFLEXORS INFLUENCES THE PROPULSIVE STRATEGY USED TO INCREASE WALKING SPEED POST-STROKE

Abstract

Objective: A deficit in paretic limb propulsion has been identified as a major biomechanical factor limiting walking speed after stroke. The purpose of this study was to determine the influence of corticomotor symmetry between paretic and nonparetic plantarflexors on the propulsive strategy used to increase walking speed.

Methods: Twenty-three participants with post-stroke hemiparesis underwent transcranial magnetic stimulation and biomechanical testing at their self-selected and fastest walking speeds. Plantarflexor corticomotor symmetry (CS_{PF}) was calculated as a ratio of the average paretic versus nonparetic soleus motor evoked potential amplitude. The ratio of the paretic and nonparetic peak ankle plantarflexion moments (PF_{sym}) was calculated at each speed.

Results: CS_{PF} predicted the ΔPF_{sym} from self-selected and fastest speeds (R^2=.629, $F_{1,21}$=35.56, p<.001). An interaction between CS_{PF} and ΔPF_{sym} (β=.596, p=.04) was observed when predicting Δspeed ($_{adj}R^2$=.772, $F_{3,19}$=20.48, p<.001). Specifically, the

ΔPF_{sym} with speed modulation was positively related to the Δspeed (p=.03) in those with greater CS_{PF}, but was not related in those with poor CS_{PF} (p=.30).

Conclusions: Symmetry of the corticomotor input to the plantarflexors influences the propulsive strategy used to increase post-stroke walking speed.

Significance: Rehabilitation strategies that promote corticomotor symmetry may positively influence gait mechanics and enhance post-stroke walking function.

Introduction

Following stroke, the majority of survivors are unable to regain sufficient walking function to allow for ambulation at speeds that are safe and effective for community function and participation.[159] In addition to typically slower walking speeds compared to neurologically-intact individuals, persons post-stroke are left with a reduced capacity to increase walking speeds.[159] The ability to modulate walking speed is clinically meaningful because it underlies an individual's capacity for safe and effective community function.[130,159] Altered muscular strength and coordination leads to asymmetrical gait patterns that underlie post-stroke hemiparesis and limit walking function.[160-163] In addition to biomechanical impairments, neurophysiologic measures of corticomotor pathway integrity to the lower extremity muscles have been shown to be related to lower extremity strength[164] and walking function post-stroke.[39,40,115]

A critical factor in producing functional walking speeds is the ability to generate sufficient propulsion to advance the body's center of mass forward.[95] In fact, the most significant biomechanical contributor to limited post-stroke walking speeds

has been identified as a deficiency in propulsive force generated by the paretic limb.[71,74,95,160] Knowledge of an individual's paretic plantarflexor contribution to forward propulsion can distinguish him or her between functional ambulation classifications of limited versus unlimited community ambulators.[74,75] Further, rehabilitation strategies that improved paretic limb propulsion have also improved post-stroke walking function.[77] The two main contributors to forward propulsion are trailing limb angle and ankle plantarflexion moment.[165,166] The plantarflexion moment represents the net torque generated by the plantarflexor muscles that cross the ankle joint. Thus, the ability to activate the plantarflexor muscles plays a critical role in generating propulsion to attain and increase gait speeds in both neurologically-intact[166] and stroke populations.[74,161,165]

Although impaired paretic propulsion has been shown to be related to post-stroke walking function, analyzing the biomechanical strategies that individuals use to *increase* their gait speed reveals important impairments of walking function.[130] In the presence of an inability to recruit the paretic plantarflexors, persons with post-stroke hemiparesis utilize a variety of compensatory strategies to achieve faster walking speeds. These include utilization of the paretic hip flexors[130,160] and compensation with the nonparetic limb.[130] Amongst a heterogeneous stroke patient population, individuals may utilize different mechanisms (e.g. increase paretic plantarflexion moment or increase reliance on nonparetic plantarflexion moment) to achieve similar walking speeds.[167] Previously, Jonkers et al found that individuals who walked at slower speeds did not use paretic plantarflexion power to increase gait speed, but instead relied on increased nonparetic plantarflexion power.[130] In contrast, individuals who walked at faster speeds increased both paretic and nonparetic plantarflexion

power to increase gait speed, which is the strategy expected in neurologically-intact individuals.[130] However, other studies have found that propulsion asymmetry between paretic and nonparetic legs is only weakly related to walking speed and that individuals walking at the same speed exhibit varying degrees of asymmetry, with some individuals improving paretic leg propulsion contribution (improved symmetry) and others relying heavily on the nonparetic leg (worse symmetry).[71,167] Although it is clear that individuals utilize different biomechanical strategies to increase walking speed post-stroke and that such strategies are associated with the level of functional recovery, *previous research has failed to identify the underlying factors that determine the biomechanical strategy used to increase gait speed.*

Following stroke, disuse of the paretic limb coupled with heavy reliance on the nonparetic limb for functional activities have been shown to induce major cortical neuronal reconstruction[3] and influence corticomotor input to affected muscles.[99] Transcranial Magnetic Stimulation (TMS) is a noninvasive brain stimulation tool that is used to investigate the neurophysiologic components underlying post-stroke motor function and recovery by quantifying the strength of corticomotor input to specific muscles.[99] In the upper extremity, the strength of corticomotor input to the paretic arm and hand has been shown to be related to muscle activation, strength and function in individuals post-stroke[17,99] and can be used to predict an individual's ability to regain activation of those muscles and functional outcomes in response to a rehabilitation intervention.[27] Additionally, abnormally increased corticomotor input to the nonparetic limb has been observed following stroke.[23,99] The resulting corticomotor asymmetry between the paretic and nonparetic limbs has been shown to be related to poor upper extremity motor recovery.[27] Though limited at this time, evolving research

in the lower extremity has indicated that decreased corticomotor input to paretic leg muscles is related to poor function.[39,40,115,164] Additionally, a recent study from our laboratory showed that contraction of the nonparetic tibialis anterior and activation of the nonlesioned hemisphere facilitated corticomotor input to the paretic tibialis anterior in those with slow walking speeds post-stroke.[115] This suggests that there may be a maladaptive influence of the nonparetic lower extremity on paretic limb walking function. However, little is known about the role of corticomotor input to the nonparetic leg and the influence of corticomotor asymmetry between paretic and nonparetic legs on *biomechanical walking function*. Further, studies to date have failed to investigate the role of corticomotor input to the *ankle plantarflexor muscles*, the primary contributors to forward propulsion during walking.

A better understanding of possible interactions between biomechanical and neurophysiologic factors that affect walking function post-stroke could be crucial for the development of effective rehabilitation approaches. The purpose of this study was to investigate the influence of lower extremity corticomotor input on the propulsive strategy used to modulate walking speed post-stroke. Specifically, we aimed to determine 1) the relationship between the symmetry of corticomotor input to the plantarflexor muscles versus the changes in plantarflexion moment symmetry and 2) if symmetry of corticomotor input to the plantarflexors moderates the relationship between change in plantarflexion moment symmetry and change in walking speed. We hypothesized that there would be a positive relationship between plantarflexor corticomotor symmetry and changes in plantarflexion moment symmetry with increases in walking speed. Additionally, there will be an interaction between change in ankle plantarflexion moment and plantarflexion corticomotor symmetry, with

individuals with the most symmetrical corticomotor input to paretic and nonparetic plantarflexors improving relative paretic ankle moment contribution with increases in walking speed.

Methods

Twenty-three individuals with chronic stroke (> 6 mo.) (15 males, mean time since stroke 50±59 mo., mean age 61.5±8.4 years) and hemiparesis were recruited. All participants gave written informed consent and the protocol was approved by the University of Delaware's Institutional Review Board. Participants sustained a single cortical or subcortical stroke, were able to walk for at least 1 minute without an orthotic and without the assistance of another person, and had sufficient ankle passive range of motion to allow the paretic ankle joint to reach the neutral position with the knee extended. Exclusion criteria included >1 previous stroke, cerebellar involvement, pain in the lower extremities, and any unsafe TMS testing criteria.[154]

Gait and clinical testing

All participants underwent biomechanical and clinical evaluations. Participants performed a 10-meter walk test to quantify self-selected and fastest walking speeds.[77] An average of 3 tests for each speed was used. Kinetic and kinematic data were collected with an 8-camera motion capture system (Motion Analysis 3D Eagle, Santa Rosa, CA) while participants walked at their self-selected and fastest speeds on a dual-belt treadmill (Bertec Corp., Columbus, OH, USA) for a total of 1 minute at each speed.[77] The treadmill was instrumented with 2 independent 6 degree of freedom force platforms that measured ground reaction forces at 1080 Hz.

Assessment of Corticomotor Input to Plantarflexors

Monophasic magnetic stimuli with a 100μs approximate rise time and a 1.0ms total duration were delivered using a magnetic stimulator (Magstim 200^2, MagStim Ltd., Wales, UK) through a custom batwing coil (maximal output 2 Tesla, each wing 11 cm in diameter, angle between windings 65˚). Participants wore an elastic cap and were seated upright comfortably with knee and ankle angles positioned at 90 degrees and both feet resting on the floor. EMG activity was recorded from double differential surface electrodes with integrated ground (BL-AE, B&L Engineering, Santa Ana, CA) that were carefully positioned and secured to the skin over the lateral soleus and tibialis anterior (TA) muscles of the paretic and nonparetic legs using a 6 channel active EMG system (BL-EMG-6, B&L Engineering, Santa Ana, CA). EMG data were sampled at a rate of 2000Hz with a 330 gain set on a 16 bit data acquisition board (National Instruments NI USB-6341), band-pass filtered at 15-450 Hz and saved for offline analysis. The experimenter began with the midpoint of the coil aligned antero-posteriorly to the vertex of the skull so that the induced electrical current traveled in the anterior direction within the cortex.[135] Stimulation began at sub-threshold intensity with the coil positioned at the vertex and gradually increased to an intensity where a visible motor evoked potential (MEP) was observed within the TA on the targeted side on real-time EMG. During the search for the optimal coil position for eliciting lower extremity MEPs, the coil was moved over the scalp as magnetic stimuli of suprathreshold intensity were delivered and participants were asked to maintain a light dorsiflexion contraction of the targeted leg while real-time EMG and MEPs from the TA were observed.[115] The optimal coil location was determined to be the location that

elicited MEPs of greatest amplitude at a given location. Approximately 20-30 stimuli were applied during the search for the optimal position for each targeted muscle for each participant. We chose to use the TA as a guide in the search for the optimal lower extremity coil location because paretic soleus MEPs could not be elicited in all participants, even when participants maintained an effortful plantarflexion contraction (see results section for full description). Our pilot testing indicated that no discernable difference in optimal coil locations existed between the TA and soleus muscles of the same leg.

The optimal location for eliciting an MEP for the paretic and nonparetic lower extremity was identified and carefully marked on the cap. Next, the setting and triggering of TMS pulses and EMG collection were performed using Custom LabVIEW software (National Instruments, Austin, TX). Throughout the trial, participants maintained a light plantarflexion contraction at 15% of their maximal volitional soleus EMG activity produced during a maximal voluntary isometric contraction. Real-time EMG biofeedback was provided to assist participants in maintaining a constant level of muscle activity. If a participant was unable to produce or maintain a 15% contraction, they were asked to produce an observable increase in EMG that they could maintain. Participants were allowed to rest if they reported fatigue or if a notable decrease in muscle activity was observed. TMS pulses were applied at intervals of 3% of the stimulator's output intensity from subthreshold through 100% maximum output intensity at a frequency of 0.2 Hz to produce a stimulus-response curve [136,137]. Only MEP responses to 100% MSO are presented

here. An additional 10 pulses were delivered at 100% maximum stimulator output intensity to each muscle.

All MEP amplitudes were normalized to the maximal response to peripheral nerve stimulation (Mmax). The tibial nerve was located in the popliteal fossa and stimulated using a custom electrical stimulator to activate the soleus muscle. Surface stimulation was delivered to the nerve using 1 ms square electrical pulses of gradually increasing intensities until no increase in the M-wave was observed within the soleus muscle. The same testing procedures were performed for the paretic and nonparetic soleus muscles.

Data Reduction and Analyses:

Cortex and Visual3D software programs (C-Motion Inc., Bethesda, MD, USA) were used for data processing. Kinematic and kinetic data were filtered using a bi-directional Butterworth low-pass filter at 6 and 30 Hz, respectively. Peak ankle plantarflexion moment resolved into the shank coordinate system was calculated for each limb during the stance phase of gait. An average of the peak plantarflexion moment for each limb was taken for all strides for each subject during two 30-second walking bouts at each speed.

Peak ankle plantarflexion moment was the biomechanical variable of interest in this study due to its temporal correlation with peak soleus muscle EMG activity during walking,[168,169] its relationship to self-selected and fastest walking speeds,[170] and, in contrast to plantarflexion power or anterior ground reaction forces, its relative independence from other joint segments (e.g. hip flexion moment on ankle joint power

or the trailing limb position on anterior ground reaction forces).[165,166] Ankle plantarflexion moment symmetry (PF_{sym}) was calculated for each participant at each speed as the average paretic plantarflexion moment divided by the average nonparetic plantarflexion moment. Change in PF_{sym} (ΔPF_{sym}) was calculated for each participant as the difference in PF_{sym} between self-selected and fast speeds.

Soleus muscle pre-stimulus EMG was measured to ensure that all subjects maintained appropriate EMG activity during plantarflexion contraction. The root-mean squared of the pre-stimulus EMG was calculated during a 100ms window prior to the stimulus artifact for each MEP used for analysis.[29,138] Trials were discarded from analysis if the EMG activity was not at least 15μV in amplitude *and* 2.5 standard deviations greater than during rest (10μV) and/or EMG activity in the contralateral muscle was greater than resting (10μV). Additionally, trials were discarded if EMG activity in the active limb was 2.5 standard deviations greater than the mean EMG activity of the trial. Raw pre-stimulus EMG values of each muscle for all subjects and pre-stimulus EMG values normalized to maximum EMG activity during an maximum volitional contraction of each muscle are shown for a select number of subjects in Appendix A (see Figure A-3.).

MEP amplitude was quantified as the peak-to-peak value of the EMG response within a 100ms window duration beginning at 10ms post stimulus artifact. Using this method, MEP amplitude is a continuous variable. For each participant, the average of the normalized, peak-to-peak MEP amplitudes at 100% of the magnetic stimulator output intensity (MEP_{100}) was determined for each the paretic and nonparetic soleus

muscles. Symmetry of the corticomotor input to the plantarflexors (CS_{PF}) was calculated for each participant as the paretic soleus MEP_{100} divided by the nonparetic soleus MEP_{100}. For both measures of symmetry, a value of 1.0 indicates perfect symmetry, with the paretic and nonparetic values being equal in magnitude; a value greater than 1 indicates the paretic was greater than the nonparetic; a value less than 1.0 indicates the paretic was less than the nonparetic.

Simple linear regression was first used to evaluate the relationship between the ΔPF_{sym} observed between participants' self-selected and fast walking speeds and CS_{PF}. Next, bivariate correlations between CS_{PF}, ΔPF_{sym}, and change in walking speed were evaluated. Subsequently, moderated multiple linear regression was used to evaluate how CS_{PF} moderated the relationship between ΔPF_{sym} and Δwalking speed. Specifically included in the model were CS_{PF}, ΔPF_{sym}, and the interaction $CS_{PF} \times \Delta PF_{sym}$. Briefly, the relationship between ΔPF_{sym} and Δwalking speed were compared for participants with good (symmetry=1.0) and poor (symmetry=0.0) CS_{PF}. All analyses were performed using SPSS version 22 with α set to 0.05.

Results

Complete data sets were obtained for all 23 participants (see Table 4-1). Consistent presence of MEPs, traditionally defined as MEPs with an amplitude of greater than 50 microvolts in more than 50% of trials,[152,171] could not be defined in the paretic soleus muscle in 7 out of the 23 participants, despite stimulation at 100% MSO. Out of these 7 participants, 4 produced small (<50 microvolts) but consistent (>50% of trials) MEPs with stimulation intensity at 100% MSO. In 3 other participants no observable MEP could be produced in the paretic soleus muscle (see Table 4-1). However, we thought that it was important to include these participants,

as they generally represented individuals of the lowest functional levels (self-selected gait speed 0.40±0.32 m/s). For this reason we chose to use a TMS outcome measure that would allow us to treat MEP amplitude as a continuous variable using a constant stimulator output intensity across all participants (i.e. 100% MSO). Thus, we were able to calculate CS_{PF} symmetry for all participants by using MEP amplitude within this time window, regardless of the size of the MEP. For the 3 participants for whom no observable MEP of any size could be elicited, the EMG activity within the observed cortical silent period was used, a value very close to zero. Example data from participants with good and poor corticomotor symmetry are presented in Figure 4-1. Optimal coil placement was found to be 1.8±.7cm anterior and 1.5±2.2cm contralateral to the vertex in the paretic leg and 2.0±.8cm anterior and 2.5±.8cm contralateral to the vertex in the nonparetic leg. In 2 participants (S20 and S22) the optimal coil positon for the paretic leg was found to be centered over the ipsilateral (contralesional) hemisphere. Optimal coil locations for the paretic and nonparetic legs of all other participants were consistently found to be centered over the contralateral hemisphere of the targeted muscle.

Participants' CS_{PF} explained 63% of the variance in the ΔPF_{sym} observed when participants increased their walking speeds ($F_{1,21}$=35.56, p<0.001, R^2=0.629) (Figure 4-2). Although ΔPF_{sym} was positively correlated to Δwalking speed (r=0.36, p=0.05) (Figure 3), CS_{PF} was not (r=0.32, p=0.07). Interestingly, neither ΔPF_{sym} (β=-0.26, p=0.30) nor CS_{PF} (β=-0.04, p=0.89) independently explained the observed Δwalking speed when accounting for the interaction between these two variables (β=0.60, p=0.04). Specifically, CS_{PF} was found to moderate the relationship between ΔPF_{sym} and Δwalking speed ($_{adj}R^2$=0.77, $F_{3,19}$=20.48, p<0.001). The model predicted a strong

positive relationship (p=0.03) between ΔPF_{sym} and Δwalking speed in individuals with high levels of corticomotor symmetry (symmetry=1.0), indicating that those individuals with greatest CS_{PF} increase their walking speed by improving the contribution of their paretic ankle moment relative to their nonparetic ankle moment. There was a non-significant negative relationship (p=0.30) between ΔPF_{sym} and Δwalking speed in those with poor corticomotor symmetry (symmetry=0.0), indicating that those individuals with poor CS_{PF} and a paretic soleus MEP_{100} equal to zero tended to increase their walking speed by *decreasing* the contribution of their paretic ankle moment relative to their nonparetic ankle moment (Figure 4-4).

Discussion

This study provides novel evidence that the balance of corticomotor input to the paretic and nonparetic plantarflexor muscles is an underlying factor that influences the biomechanical strategy used to increase walking speed in individuals post-stroke. Specifically, we observed that more symmetrical corticomotor input to the paretic and nonparetic plantarflexor muscles was associated with increases in PF_{sym} when walking at faster speeds (see Figure 4-2). Additionally, we found that participants with low levels of corticomotor symmetry to plantarflexors were not likely to increase walking speed through more symmetrical plantarflexor moments, but those with high levels of corticomotor symmetry to plantarflexors were (see Figure 4-4). These findings reveal how the neurophysiologic characteristics of individuals with chronic stroke may influence the biomechanical strategies used to increase walking speed. These results thus have important implications for post-stroke rehabilitation.

Consistent with previous literature, changes in PF_{sym} were weakly correlated to changes in walking speed.[71,167] Nonetheless, change in PF_{sym} and CS_{PF} alone were not

significant predictors of change in walking speed. Our data suggest that, despite having poor changes in PF_{sym} and poor CS_{PF}, some individuals were still able to sufficiently increase walking speed through reliance on the nonparetic limb (see Table 4-1). However, the *interaction* between change in PF_{sym} and CS_{PF} was the only significant predictor of change in walking speed. In the present study, individuals with good CS_{PF} generally increased their paretic plantarflexion moment (see Table 4-1), leading to improvements in PF_{sym} to reach their fastest walking speed (see Figure 4-4). Information about the symmetry of the corticomotor input to the plantarflexors thus appears to provide information about the *capacity* to improve the paretic limb's contribution to propulsion in post-stroke ambulation. Our data suggest that those with greater corticomotor symmetry possess sufficient intact corticomotor pathways to allow for increased paretic plantarflexor recruitment to meet the increased propulsive demands required for faster walking speeds.[165,166] In contrast, individuals with poor corticomotor symmetry seem to possess weaker corticomotor pathways to the paretic plantarflexors and may have saturated their ability to recruit paretic plantarflexors at slower self-selected gait speeds.[130] These individuals were, therefore, forced to rely on nonparetic plantarflexors and other compensatory strategies to increase propulsion when walking at faster speeds. The lack of significance in the relationship between change in PF_{sym} and change in walking speed in individuals with poor CS_{PF} could be because these individuals adopt a variety of compensation strategies in addition to the increased nonparetic plantarflexion moment. For example, increases in trailing limb angle[165] or hip flexion power[130,160] with walking speed modulation could introduce variability to this relationship. The results of this study indicate that changes in biomechanical patterns alone are not sufficient to accurately predict changes in

walking speed, but that knowledge of the balance of corticomotor input to each limb is critical for predicting functional ambulation ability.

This is the first study to investigate the relationship between plantarflexor corticomotor excitability measures and the kinetics of walking in individuals post-stroke. Indeed, this is a challenging area of research when utilizing traditional measures of corticomotor excitability. Previous studies with stroke have utilized corticomotor excitability measures that were a function of TMS motor threshold.[164,172-174] This approach has been particularly challenging in lower extremity muscles such as plantarflexors that receive less cortical input and have higher motor thresholds.[7,175] Thus, likely due to methodological limitations, we are not aware of any studies that have previously studied post-stroke corticomotor measures in the soleus, a muscle that plays a crucial role in generating propulsion during walking. Such conventional methods that rely on use of motor threshold do not allow for the inclusion of the most impaired participants, who typically have the highest motor thresholds (i.e. >90%MSO) or have absent MEPs in the paretic leg. By utilizing a reliable method (see Appendix B, Table B-1) where a constant intensity is used across subjects, we were able to collect data for all participants, including those without the presence of an MEP response in the paretic soleus muscle. For these participants, their corticomotor symmetry values were close to zero, enabling our model to predict the propulsion strategy used to increase walking speed in individuals across the full spectrum of asymmetries. Future studies aiming to study post-stroke individuals of low-level function may consider utilizing such measures.

Results of this study show that symmetry of corticomotor input to the lower extremity is related to gait impairments and influences kinetics of walking function in

individuals with chronic stroke. Thus, the corticomotor patterns of lower extremity motor recovery appear similar to those of the upper extremity.[23,27] Previous research has suggested that rehabilitation does not sufficiently target the function of the paretic limb and generally leads to strengthening of compensation strategies instead of learning to utilize more optimal gait patterns, limiting functional outcomes.[82] Reliance on ankle-foot orthoses or assistive devices commonly used in neurologic rehabilitation immobilizes and promotes disuse of the paretic limb, leading to further degradation of paretic limb function.[3] Indeed, heavy reliance on one limb coupled with disuse of the other limb is related to major cortical neuroplastic changes that lead to corticomotor imbalances.[3,27] Interestingly, learning new motor skills can increase corticomotor input to paretic limb muscles and decrease input to the nonparetic limb muscles, promoting greater corticomotor symmetry.[27,84] It is possible that rehabilitation strategies that promote disuse of the paretic leg strengthen compensation with the nonparetic leg, resulting in an imbalance of corticomotor input to paretic and nonparetic plantarflexors. Future research could determine if rehabilitation strategies shown to promote corticomotor symmetry in the upper extremity[27] can also improve corticomotor balance in the lower extremity and lead to positive changes in gait biomechanical and walking function.

Limitations:

Due to the cross-sectional design of the present study, it is not clear if corticomotor imbalances lead to biomechanical impairments or if they result from observed compensation strategies. In this study, measures of plantarflexion moment were reported because of its specificity to the plantarflexor muscle contribution to propulsion. However, we did not investigate other factors that could also affect

propulsion and influence gait speed, such as the position of the trailing limb during late stance, which could explain additional variability in the model. In lower extremity TMS experimentation, the anatomy of lower extremity muscle representation within the motor cortex makes it improbable that one hemisphere can be stimulated in isolation, particularly at high stimulator output intensities. Thus, it is difficult to discern differential hemispheric contributions to the observed corticomotor asymmetries. Additionally, because optimal coil locations for the paretic leg in 2 participants were found to be centered over the ipsilateral hemisphere relative to the vertex, it is possible that different corticomotor mechanisms (e.g. coticomotor pathways from the contralesional hemisphere to the paretic soleus) contributed to symmetry of corticomotor input between paretic and nonparetic plantarflexors. Future research utilizing imaging techniques could provide important and more precise spatial information about cortical origins of motor pathways to the paretic limb and its effect on walking recovery. In this study the TA muscle was used to identify the location for coil positioning in this study and it is possible that this location was not the best for stimulation of the soleus muscle and may have decreased the actual value for soleus MEP_{100}s. However, our pilot testing showed there was no discernible difference between the optimal coil locations of the TA and soleus muscle of the same leg. If this did occur, then coil position would likely affect both the paretic and nonparetic soleus MEP_{100}s and would likely have minimal effect on the soleus corticomotor symmetry value. All corticomotor data in the present study were collected while participants were seated and it is possible that the strength of corticomotor input could change with walking. All participants in the present study

were able to walk without an orthosis or assistance of another person, making results ungeneralizable to all individuals post-stroke.

Conclusions

The present study provides novel evidence that symmetry of corticomotor input to the lower extremity muscles of persons post-stroke underlies gait impairments and influences walking function. Measures of corticomotor input may assist clinicians in identifying the most effective rehabilitation strategies for each individual to maximize walking function post-stroke. Post-stroke gait rehabilitation interventions should target strategies to promote symmetry of corticomotor input to the plantarflexor muscles to enhance biomechanical contributions from the paretic lower extremity during walking

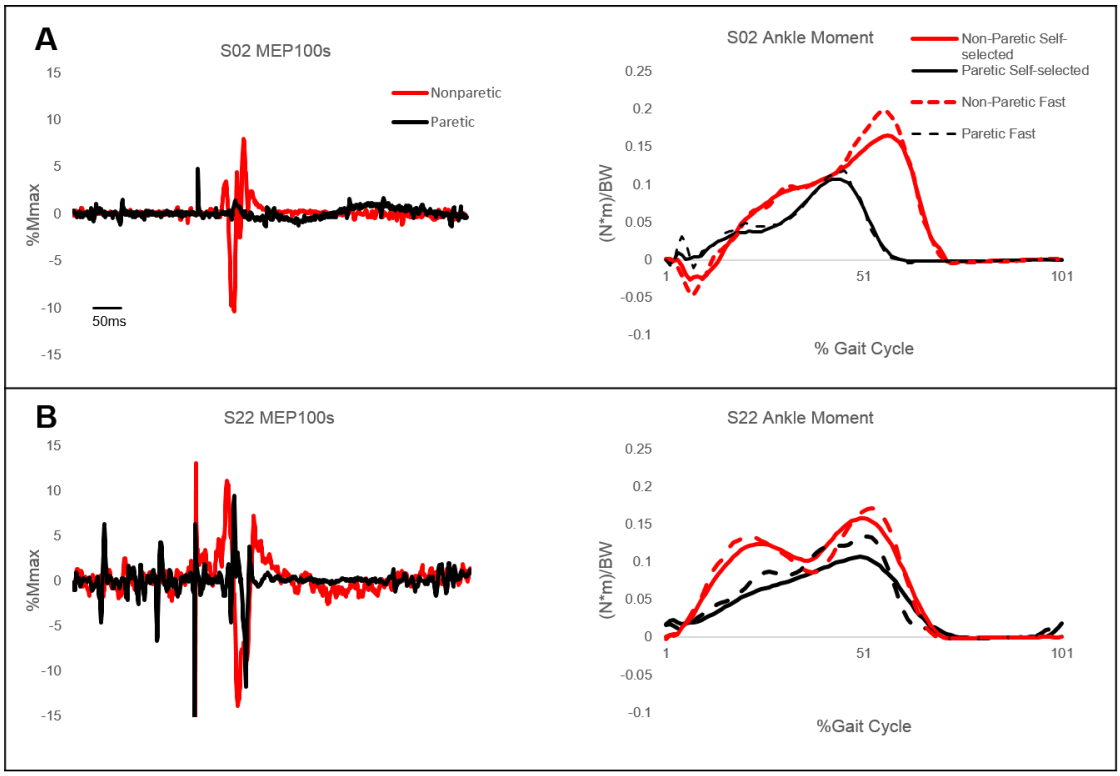

Figure 4-1. Raw soleus MEP_{100} data (left column) and mean plantarflexion moments over all strides for paretic and nonparetic legs (right column) are shown for a participant with poor (A) and good (B) corticomotor symmetry. [139] *doi: 10.1016/j.clinph.2015.12.003.*

*Table 4-1. Individual participant (N=23) gait speeds, MEP_{100} (%Mmax), and plantarflexion moment results. (CS_{PF} = corticomotor symmetry of plantarflexors; PF = plantarflexion ankle moment; PF_{sym} = symmetry of plantarflexion ankle moment). ɾ indicates that the observable MEP was < 50 microvolts. * indicates that no observable MEP was detected. ∞ indicates that the optimal location for stimulating the paretic leg was found to be centered over the ipsilateral hemisphere.*[139] *doi: 10.1016/j.clinph.2015.12.003.*

Participant No.	Self-selected gait speed (m/s)	Fast gait speed (m/s)	Paretic MEP_{100} (%Mmax)	Nonparetic MEP_{100} (%Mmax)	CS_{PF}	Self-selected Speed			Fast Speed			
						Paretic PF	Nonparetic PF	PF_{sym}	Paretic PF	Nonparetic PF	PF_{sym}	Change PF_{sym}
01	1	1.1	7.3	10.0	0.726	0.127	0.156	0.815	0.126	0.161	0.782	-0.034
02[1]	1.07	1.51	1.6	15.8	0.099	0.115	0.187	0.613	0.128	0.235	0.543	-0.070
03	1	1.32	8.5	11.8	0.717	0.101	0.142	0.708	0.113	0.134	0.841	0.132
04	0.74	0.85	4.1	29.0	0.140	0.061	0.083	0.731	0.066	0.097	0.681	-0.050
05	1.13	1.37	1.3	32.4	0.040	0.142	0.162	0.876	0.124	0.160	0.777	-0.099
06	1.16	1.59	5.6	15.6	0.359	0.126	0.154	0.814	0.140	0.173	0.806	-0.008
07	1.44	1.55	4.0	6.6	0.606	0.122	0.122	1.001	0.130	0.121	1.077	0.076
08	0.94	1.11	1.1	7.3	0.152	0.122	0.118	1.031	0.121	0.129	0.935	-0.096
09	0.92	1.05	4.7	15.8	0.299	0.118	0.147	0.803	0.120	0.153	0.783	-0.019
10	1.01	1.11	17.5	25.4	0.689	0.145	0.128	1.140	0.153	0.131	1.170	0.030
11	0.35	0.83	5.4	7.4	0.728	0.072	0.131	0.547	0.108	0.162	0.665	0.118
12[1]	0.18	0.6	3.6	12.5	0.283	0.062	0.131	0.474	0.063	0.134	0.466	-0.008
13	0.26	0.38	3.4	4.5	0.753	0.061	0.083	0.736	0.068	0.095	0.721	-0.016
14[1]	0.32	0.38	5.0	16.7	0.297	0.000	0.072	0.000	0.000	0.076	0.000	0.000
15*	0.32	0.33	0.3	25.5	0.012	0.000	0.046	0.000	0.000	0.051	0.000	0.000
16[1]	0.09	0.24	1.8	10.0	0.177	0.001	0.055	0.016	0.000	0.055	0.000	-0.016
17*	0.4	0.51	0.7	11.8	0.060	0.102	0.111	0.915	0.101	0.119	0.854	-0.061
18*	0.43	0.96	0.9	12.6	0.068	0.115	0.161	0.715	0.116	0.169	0.686	-0.029
19	0.45	0.78	8.0	8.2	0.981	0.060	0.099	0.605	0.085	0.112	0.765	0.159
20[∞]	0.53	0.73	12.8	27.8	0.459	0.115	0.130	0.888	0.126	0.145	0.870	-0.018
21	1	1.37	15.4	13.2	1.166	0.121	0.121	0.995	0.152	0.140	1.088	0.094
22[∞]	0.6	0.9	18.3	20.9	0.876	0.131	0.163	0.806	0.158	0.175	0.901	0.095
23	0.81	1.1	6.7	9.1	0.734	0.137	0.141	0.977	0.151	0.147	1.024	0.047

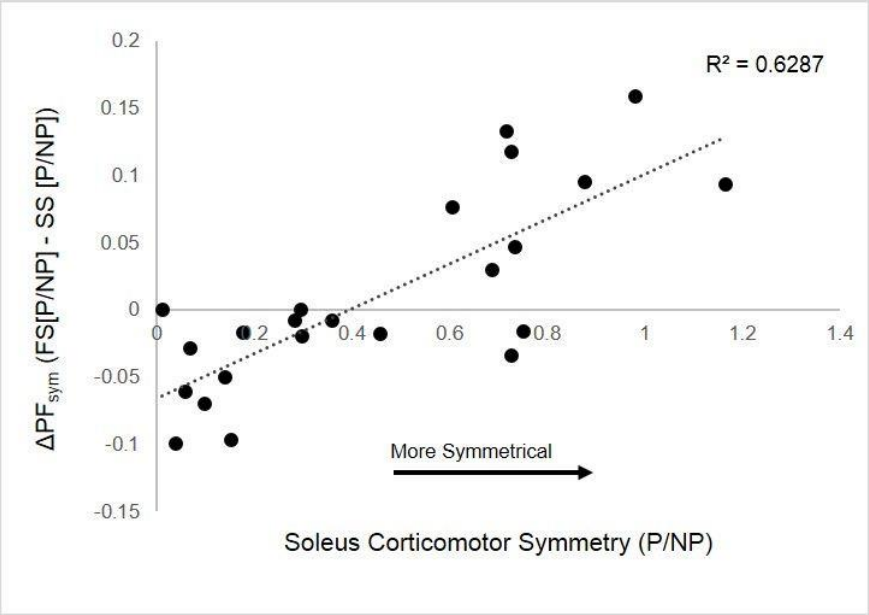

Figure 4-2. The relationship between corticomotor symmetry (paretic (P) MEP_{100}/nonparetic (NP) MEP_{100}) and change in plantarflexion moment symmetry (ΔPF_{sym}) (paretic plantarflexion moment/nonparetic plantarflexion moment) from self-selected (SS) to fastest walking (FS) walking speed ($F(1,21)=35.56$, $p<0.001$, $R^2=0.629$) (n=23). P: paretic; NP: nonparetic; ΔPF_{sym}: change in plantarflexion ankle moment symmetry; FS: fast walking speed; SS: slow walking speed. [139] *doi: 10.1016/j.clinph.2015.12.003.*

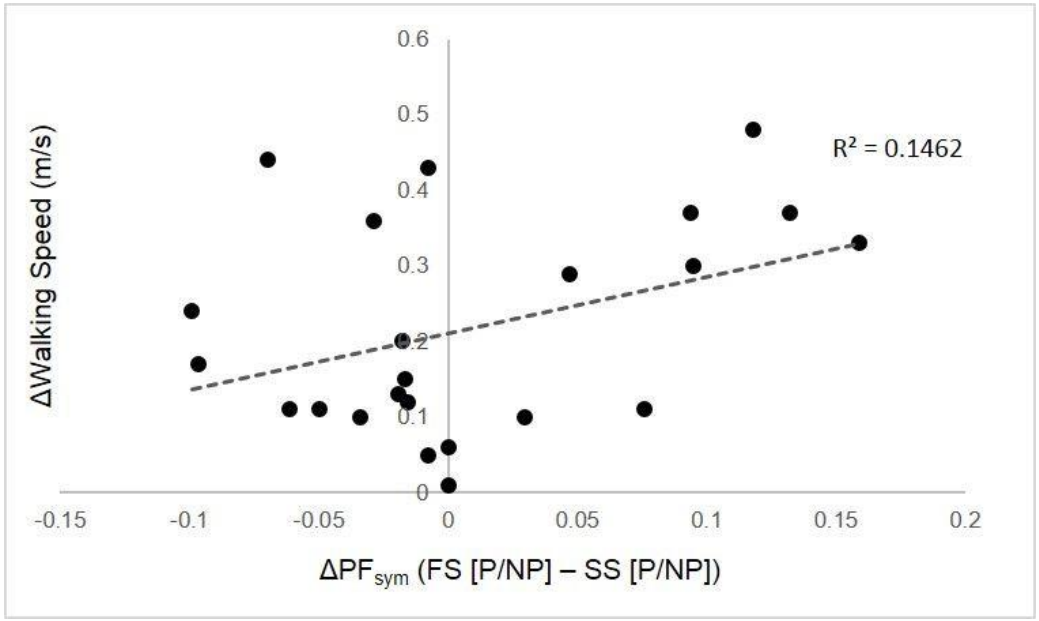

*Figure 4-3. The relationship between change in plantarflexion moment symmetry (ΔPF_{sym}) (paretic (P) plantarflexion moment/nonparetic (NP) plantarflexion moment) from self-selected (SS) to fastest walking (FS) speed and change in walking speed (FS-SS) (*r=*0.36,* p=*0.05) (n=23). P: paretic; NP: nonparetic; ΔPF_{sym}: change in plantarflexion ankle moment symmetry; FS: fast walking speed; SS: slow walking speed.* [139] *doi: 10.1016/j.clinph.2015.12.003.*

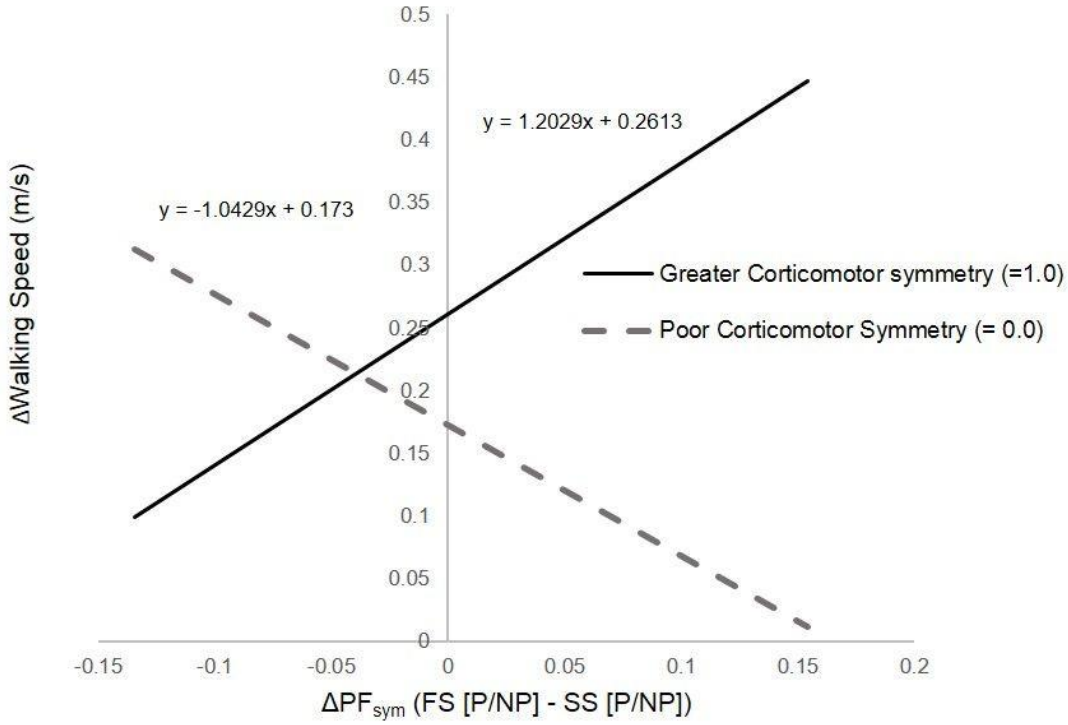

*Figure 4-4. Moderation effect of corticomotor symmetry on the relationship between change in plantarflexion moment symmetry from self-selected to fastest walking speed (ΔPF_{sym}) (±2 standard deviations from the mean) and change in walking speed. There was a positive relationship (*p*=0.03) between ΔPF_{sym} and change in walking speed in individuals with high levels of corticomotor symmetry (symmetry=1.0) and a non-significant negative relationship (p=0.30) between ΔPF_{sym} and Δwalking speed in those with poor corticomotor symmetry (symmetry=0.0). P: paretic; NP: nonparetic; ΔPF_{sym}: change in plantarflexion ankle moment symmetry; FS: fast walking speed; SS: slow walking speed.* [139] *doi: 10.1016/j.clinph.2015.12.003.*

Chapter 5

CHANGES IN CORTICOMOTOR DRIVE TO PLANTARFLEXORS SEEN FOLLOWING A SINGLE SESSION OF GAIT TRAINING WITH FUNCTIONAL ELECTRICAL STIMULATION ARE RELATED TO CHANGES IN ANKLE MOMENT IN INDIVIDUALS POST-STROKE

Abstract

Objective: Functional electrical stimulation (FES) can induce positive cortical and biomechanical changes in individuals post-stroke and improve walking function. Though individual patient responses to FES application in clinical settings are variable, there is emerging evidence that neuroplasticity that occurs in response to a single session of rehabilitation is predictive of long-term functional outcomes. While use of multiple sessions of FES were shown to induce cortical plasticity related to functional outcomes in the upper extremity post-stroke, our knowledge of FES-induced cortical plasticity in the lower extremity is limited and neural responses to FES within a single session of rehabilitation are unknown. The purpose of this study was to 1) test the effectiveness of a session of FES gait training to improve plantarflexion ankle moment symmetry and corticomotor symmetry of plantarflexor muscles and 2) determine if changes in corticomotor drive are related to changes in ankle moment within the session.

Methods: Twenty individuals with chronic stroke completed two identical sessions of treadmill walking; one session included FES to the dorsi- and plantarflexor muscles

(FESW) and the other session did not use FES (NoFESW). Kinetic and kinematic data were collected during treadmill walking pre and post-training for each session. Peak plantarflexion ankle joint moments were calculated for the paretic and nonparetic limbs during the stance phase of gait and used to calculate ankle moment symmetry. Transcranial magnetic stimulation (TMS) was used to elicit motor evoked potentials (MEPs) from the paretic or nonparetic soleus muscles. Plantarflexor corticomotor symmetry was calculated as the average paretic MEP amplitude divided by the average nonparetic MEP amplitude.

Results: There was a positive change in corticomotor symmetry that was related to change in ankle moment symmetry following FESW. Corticomotor drive to the paretic soleus showed an increase following FESW that was positively correlated to change in paretic ankle moment. Corticomotor symmetry and ankle moment symmetry decreased following NoFESW; these changes were not related to each other

Conclusions: Findings of this study demonstrate the effectiveness of FES gait training to induce cortical plasticity to plantarflexor muscles to improve biomechanical walking function and provide insight into mechanisms of cortical plasticity underlying biomechanical improvements. Further, results show that neuroplastic changes in lower extremity motor cortical areas are detectible following a single session of rehabilitation. Future studies are needed to determine if the corticomotor responses to a single session of rehabilitation predicts a patient's functional outcome to long-term intervention.

Introduction

Restoration of walking function following stroke is one of the primary goals of stroke survivors.[176] However, despite often intensive rehabilitation efforts, the majority of stroke survivors will never achieve walking speeds that allow for safe and effective community function.[103,104] The failure of conventional rehabilitation strategies to effectively regain post-stroke walking ability likely results from our lack of understanding of the neural mechanisms underlying motor recovery[124] combined with inadequately targeting key biomechanical factors that limit walking speed and economy.[81,129,140]

In the presence of lost function following brain injury, one of the most common and consistent observations is that individuals develop compensatory strategies to perform daily activities such as walking.[177,178] Indeed, hemiparesis affects approximately 90% of all stroke survivors.[177] Often, with an initial goal to regain walking ability as quickly as possible, individuals utilize inefficient compensation strategies such as stiff-legged and circumducted gait to advance the paretic limb,[66] heavily increasing the reliance on the nonparetic limb to generate propulsive force.[179] Reduced paretic limb propulsive force and ankle power have been consistently identified by previous research to be the most significant contributors to walking speed impairments[9,130] and can determine whether an individual is categorized as a limited community or unlimited community ambulator.[75] The resulting asymmetrical gait patterns increase the energy cost of walking,[68] limiting endurance and community function.[178] Interestingly, such compensations continue in the chronic phase of motor

recovery, even when the capacity to regain paretic limb function may exist.[180] When effectively improved, paretic limb propulsion can increase post-stroke walking function.[77,78] However, the neural factors limiting these biomechanical determinants of post-stroke walking ability and the capacity for walking recovery are poorly understood, creating a barrier to current rehabilitation approaches.

Non-use in one extremity coupled with heavy reliance on the contralateral extremity has been shown to result in major imbalances of cortical excitation and inhibition.[83,101,147] In the upper extremity, a decrease in corticomotor activity in the lesioned hemisphere coupled with over-activity in the nonlesioned hemisphere has been consistently observed.[23,107,108,141] Unlike neurologically-intact individuals, enhanced cortical activity in the ipsilateral nonlesioned hemisphere is commonly observed during paretic limb movement in stroke survivors.[181,182] The resulting hemispheric imbalance and asymmetry of corticomotor input to the paretic and nonparetic arm and hand has been shown to be related to poor motor recovery.[27,30,109] Additionally, post-stroke disruptions in interactions between afferent input to the somatosensory cortex and efferent motor neurons within the primary motor cortex have a large influence over the balanced pattern of cortical excitation and inhibition that is essential for motor function.[15] Alterations in afferent input to one hemisphere have been shown to profoundly affect both cortical hemispheres[52,53] and may also explain observed patterns of cortical disinhibition to the nonlesioned hemisphere following stroke.[51] Resulting interhemispheric imbalances likely exacerbate asymmetry of corticomotor input to paretic and nonparetic limbs and affect movement

patterns.[112,183] Recently, work from our laboratory found that corticomotor symmetry to plantarflexor muscles predicted the biomechanical propulsive strategy that stroke survivors used when asked to increase walking speed.[139] Specifically, individuals with the *greatest corticomotor symmetry* between limbs increased their walking speed by improving propulsive contribution of the paretic leg, *reducing* propulsive asymmetries between limbs. Individuals with the *least corticomotor symmetry* increased their walking speed by increasing reliance on propulsive contribution of the nonparetic leg, *magnifying* their gait asymmetries. It is conceivable that rehabilitation strategies that promote improvements in corticomotor balance between limbs in appropriate lower limb muscle groups could also improve biomechanical factors that limit post-stroke walking speed.[139]

It is clear that changes in brain structure and function translate to changes in motor function following stroke,[60] but it is unknown which rehabilitation strategies are most effective in inducing positive neuroplastic changes amongst a heterogeneous stroke patient population. Most conventional post-stroke rehabilitation programs address muscle strengthening, cardiovascular fitness, balance and joint range of motion and utilize ankle-foot-orthoses and assistive devices,[80,177] insufficiently targeting function of the paretic limb. This leads to further strengthening of compensatory strategies instead of learning to utilize more optimal gait patterns, limiting functional outcomes.[78,81,140] Innovative rehabilitation strategies in the upper extremity, such as constraint induced movement therapy, that have focused on improving cortical function and sensorimotor impairments and have induced changes

in cortical activity and corticomotor input to the paretic arm and hand, have achieved gains in upper extremity function beyond those of conventional rehabilitation.[60,184] Though implementation of this strategy is not feasible for the lower extremity, it may be possible to achieve similar results using other strategies to target similar sensorimotor pathways.

Functional electrical stimulation (FES) is a rehabilitation strategy that temporally couples electrical stimulation of motor and sensory nerve fibers during performance of a functional motor task and may target similar neural pathways to constraint induced movement therapy in the upper extremity to enhance motor learning.[3,86] Recently, studies using neuroimaging and noninvasive brain stimulation techniques have investigated the effect of FES on cortical function. The long-term use of FES in the paretic upper extremity during rehabilitation activities yielded changes in cortical activation patterns coupled with improved functional outcomes.[61-63,88] Specifically, patients with improved motor function showed a decrease in unaffected hemisphere activation and a shift in the focus of brain activity to the affected hemisphere during a paretic hand motor task.[61-63] In the lower extremity, long-term use of FES to the paretic dorsiflexors during gait induced an increase in corticomotor input to the tibialis anterior[90] and improved timing of paretic dorsiflexor activation during walking.[89] Gandolla et al[94] showed that FES coupled with voluntary dorsiflexion increased the sensitivity of the primary somatosensory cortex selectively to primary motor cortex projections, demonstrating the ability for FES to target neural connections critical for motor control. Together these studies provide strong evidence

for the potential effectiveness of the use of FES to induce positive neuroplasticity and show that FES targets the potentially maladaptive cortical pathways associated with poor motor function following stroke. Interestingly, literature reviews to date on the topic of FES to improve walking function in stroke survivors have concluded that compared to matched treatments, FES was *not* superior in enhancing functional ambulation improvement[11,96] creating further ambiguity on the effectiveness of FES in inducing neuroplasticity that translates to improved function.

Insignificant findings and failed clinical trials for improving walking function in the stroke patient population have not just occurred with FES therapies, but with a number of different types of intervention strategies.[185-187] We posit that this is likely due to lack of targeting of key biomechanical walking impairments and neurophysiologic substrates coupled with the heterogeneity of impairments in stroke patient populations. Recent work from our laboratory showed that when post-stroke gait training interventions targeted biomechanical propulsion impairments of the paretic limb, chronic stroke survivors were able to make substantially greater gains in walking speed than had been reported in previous studies.[77] Further, when plantarflexor motor impairments were specifically targeted with FES, this specifically resulted in improved paretic ankle moment in individuals who showed propulsive improvements.[188] Though these results were promising, amongst a heterogeneous stroke patient population responses to FES gait training were variable, possibly secondary to limited neural capacity for paretic limb motor improvement in some stroke survivors.[99]

Though targeting improvements in the paretic limb's contributions to ambulation through the use of an intervention such as FES may be an effective treatment strategy for some patients, it is unlikely to be the optimal strategy for all patients. In response to an intervention utilizing FES to the paretic upper extremity, Page et al[97] observed an *opposite* change in cortical activation patterns in participants with versus without active extension of the fingers or wrist. The participants without active wrist extension showed an *increase* in activity of the nonlesioned hemisphere and no improvements in motor function.[97] Discrepancies of patterns of corticomotor changes and upper extremity motor improvements between low-level[97] and higher-level patients[61-63] suggest that a neural substrate that enables some voluntary activation of the paretic extremity muscles may be essential to make functional motor gains through use of FES.[98] Thus, it is essential to identify potential biomarkers and individuals who are most likely to show a positive response to specific intervention strategies. Though baseline measures of corticomotor symmetry were found to have poor prognostic ability for therapeutic improvements in the chronic stage of stroke, *changes* in corticomotor drive to the paretic and nonparetic hand muscles in response to a single session were found to be strongly predictive of improvements in upper extremity motor functional following rehabilitation.[26] Likewise, it is possible that individuals who are able to improve corticomotor symmetry to the lower extremity muscles following a session of gait training could also show related improvements in walking mechanics.

There is a substantial gap in our understanding of the neurophysiologic underpinnings of the biomechanical limitations of post-stroke walking function,[71-74] and how changes in neural mechanisms might affect gait mechanics. Further, though single session corticomotor changes can be predictive of post-stroke long-term functional improvements,[26] no previous studies have investigated FES-induced cortical plasticity in response to a single session of rehabilitation in stroke survivors. The purpose of this study was to 1) test the effectiveness of a single session of FES gait training to improve plantarflexion ankle moment symmetry and corticomotor symmetry of plantarflexor muscles compared to a session of walking alone and 2) determine if changes in corticomotor asymmetry are related to changes in ankle moment symmetry within the session.

Methods

A cross-over repeated measures experimental design was used. The independent variable was session type (FES walking (FESW) and walking without FES (NoFESW)). Dependent variables were MEP amplitude and plantarflexion ankle moment. Additionally, pre-to-post session change values and between limb symmetry values were calculated from MEP amplitudes and ankle moments and used as dependent variables in analyses. We recruited 20 individuals with chronic stroke (> 6 mo.) (16 males, mean time since stroke 42±35 mo., mean age 59.5±12.0 years, Lower Extremity Fugl-Meyer 22±6) for this study. All participants gave written informed consent and the experimental protocol was approved by the University of Delaware's

Institutional Review Board. All participants had lower extremity hemiparesis with visually detectable gait deficits, sustained a single cortical or subcortical stroke, sufficient ankle range of motion to reach neutral with the knee fully extended, and were able to walk for at least 4 minutes on a treadmill without an orthotic and without the assistance of another person. Exclusion criteria included >1 previous stroke, cerebellar involvement, pain in the lower extremities, and any unsafe TMS testing criteria.[133]

Biomechanical Testing

All participants performed a 10 meter walk test to quantify their self-selected walking speeds.[132] An average of 3 tests was used as the participant's treadmill walking speed during biomechanical testing and gait training. Kinetic and kinematic data were collected with an 8-camera motion capture system (Motion Analysis 3D Eagle, Santa Rosa, CA) while participants walked on a dual-belt treadmill (Bertec Corp., Columbus, OH, USA) for a total of 1 minute. The treadmill was instrumented with 2 independent 6 degree of freedom force platforms that measured ground reaction forces at 1080 Hz.

Assessment of Corticomotor Excitability to Plantarflexors

A magnetic stimulator (Magstim 200^2, MagStim Ltd., Wales, UK) was used to deliver monophasic magnetic pulses with a 100μs approximate rise time and a 1.0ms total duration through a custom batwing coil (maximal output 2 Tesla, each wing 11 cm in diameter, angle between windings 65˚). All participants were seated upright in an arm chair with both feet resting on the floor and knees and ankles positioned at

approximately 90 degrees. EMG activity was recorded from double differential surface electrodes with integrated ground (BL-AE, B&L Engineering, Santa Ana, CA) that were carefully positioned and secured to the skin over the lateral soleus and tibialis anterior (TA) muscles of the paretic and nonparetic legs using a 6 channel active EMG system (BL-EMG-6, B&L Engineering, Santa Ana, CA). EMG data were sampled at a rate of 2000Hz with a 330 gain set on a 16 bit data acquisition board (National Instruments NI USB-6341), band-pass filtered at 15-450 Hz. The coil was aligned posterior-anteriorly to the vertex of the skull so that the induced electrical current traveled in the anterior direction within the cortex.[135] The coil was positioned at the vertex of the skull and stimulation began at sub-threshold intensity and gradually increased to an intensity where a visible and consistent (>50% of trials) motor evoked potential (MEP) was observed on real-time EMG within the TA on the targeted side. Suprathreshold magnetic stimuli were delivered while the coil was moved over the scalp and the experimenter searched for the "hotspot," the optimal coil position for eliciting lower extremity MEPs. During location of the hotspot, participants were asked to maintain a light dorsiflexion contraction of the targeted leg while real-time EMG and MEPs from the TA were visually observed. [115] The hotspot was determined to be the location that elicited MEPs of greatest amplitude within the targeted muscle. Typically, 20-30 stimuli were applied during the search for the hotspot for each muscle. We detected no discernable difference in hotspot locations between the TA and soleus muscles of the same leg in our pilot testing for this study. Thus, we chose to use the TA as a guide in the search for the common TA and soleus

lower extremity hotspot for each leg because TA MEPs were more pronounced than soleus MEPs, particularly in the most impaired participants.

The optimal location for eliciting an MEP for the paretic and nonparetic lower extremity was identified and carefully marked on the cap. Next, the setting and triggering of TMS pulses and EMG collection were performed using Custom LabVIEW software (National Instruments, Austin, TX). Throughout the trial, participants maintained a light plantarflexion contraction at 15% of their maximal volitional soleus EMG activity produced during a maximal voluntary isometric contraction. Real-time EMG biofeedback was provided to assist participants in maintaining a constant level of muscle activity. If a participant was unable to produce or maintain a 15% contraction, they were asked to produce an observable increase in EMG that they could maintain. Participants were allowed to rest if they reported fatigue or if a notable decrease in muscle activity was observed. TMS pulses were applied at intervals of 3% of the stimulator's output intensity from subthreshold through 100% maximum output intensity at a frequency of 0.2 Hz to produce a stimulus-response curve.[136,137] An additional 10 pulses were delivered at 100% maximum stimulator output intensity to each muscle. Only MEP responses to 100% of the maximum the stimulator's output are presented here.

All MEP amplitudes were normalized to the maximal response to peripheral nerve stimulation (Mmax). The tibial nerve was located in the popliteal fossa and stimulated using a custom electrical stimulator to activate the soleus muscle. Surface stimulation was delivered to the nerve using 1-ms square electrical pulses of gradually

increasing intensities until no increase in the M-wave was observed within the soleus muscle. The same testing procedures were performed for the paretic and nonparetic soleus muscles.

Gait training session with functional electrical stimulation

A licensed physical therapist administered all gait training sessions. Participants completed a session of FES walking (FESW) and a session of walking without FES (NoFESW) approximately one week apart. The order of each session was randomized. The FESW session consisted of five 6-minute treadmill walking bouts at the participant's self-selected gait speed. During each session, the participant wore a moveable harness attached to the ceiling for safety, but no body weight will be supported by the harness. FES was delivered through self-adhesive surface stimulation electrodes in an alternating pattern for 1-minute on and 1-minute off to the paretic ankle dorsi- and plantarflexor muscle groups (Figure 1). Two compression foot switches were attached to the sole of the shoe of the paretic limb under the lateral aspect of the fifth metatarsal head and the other on the hindfoot under the lateral portion of the heel. These foot switches were used to control the delivery of FES from a custom built stimulator. During gait, FES parameters for stimulation used variable frequency trains that consisted of a high-frequency 200 Hz 3-pulse burst followed by a lower frequency 30 Hz constant frequency train.[127] Pulse duration was set at 300μs and pulse amplitude at the intensity for reaching an ankle neutral position (dorsiflexors) and heel rise with staggered stance in weight-bearing (plantarflexors). FES to dorsiflexors muscles was delivered when the forefoot switch was turned off

(paretic toe off) until the hind foot switch was turned on (paretic heel strike). FES to plantarflexor muscles was delivered when the hind foot switch was turned off (indicating paretic heel off) and ended when the forefoot switch was turned off (indicating paretic toe off). Further details regarding the customized FES system and methods can be found in a previous study put forth by our laboratory.[127] Procedures for the NoFESW session were identical to that of the FESW session, without administration of the FES. Two 30-second bouts of post-test biomechanics were collected at the same initial walking speed immediately following the 5th bout of walking during each session. FES remained off during all biomechanical testing. TMS post-testing was completed immediately after the subject was seated in a chair following each training session.

Data Reduction and Analyses

Kinematic and kinetic data were filtered using a bi-directional Butterworth low-pass filter at 6 and 30 Hz, respectively. Biomechanical data processing was performed using Cortex and Visual3D software programs (C-Motion Inc., Bethesda, MD, USA). We calculated peak ankle plantarflexion moment resolved into the shank coordinate system for each limb during the stance phase of gait. An average of the peak plantarflexion moment for each limb was taken for all strides for each subject during two 30-second walking bouts at pre and post testing for each session. We chose to use peak ankle plantarflexion moment as the biomechanical dependent variable in this study due to its synchronized timing of occurrence with peak soleus muscle EMG

activity during walking [168,169], its relationship to post-stroke walking speed [170], and its relative independence from other joint segments (e.g. hip flexion moment on ankle joint power or the trailing limb position on anterior ground reaction forces) in contrast to plantarflexion power or anterior ground reaction forces [165,166]. Ankle plantarflexion moment symmetry was calculated for each participant at each speed as the average paretic plantarflexion moment divided by the average nonparetic plantarflexion moment.

We quantified pre-stimulus EMG from the paretic and nonparetic soleus muscles during pre- and post- testing to ensure that all subjects met appropriate EMG activity during muscle facilitation. We calculated the average root-mean squared amplitude of the pre-stimulus EMG during a 100ms window prior to the stimulus artifact for each MEP. Trials were discarded from analysis if the EMG activity of the targeted soleus muscle was not at least 2.5 standard deviations greater than during resting and/or EMG activity in the contralateral muscle was greater than during the resting condition. Additionally, trials were removed from analysis if EMG activity in the targeted soleus was not at least 15μV in amplitude *and* 2.5 standard deviations greater than the EMG activity of the muscle measured during rest. Raw pre-stimulus EMG values of each muscle for all subjects and pre-stimulus EMG values normalized to maximum EMG activity during a maximum volitional contraction are shown for a select number of subjects during pre- and post-TMS testing for each session in Appendix A (see Appendix A, Figure A-4).

MEP amplitude was quantified as the peak-to-peak value of the EMG response within a 100ms window duration beginning at 10ms post stimulus artifact. Using this method, MEP amplitude is a continuous variable.[139] For each participant, the average of the normalized, peak-to-peak MEP amplitudes at 100% of the magnetic stimulator output intensity (MEP_{100}) was determined for each the paretic and nonparetic soleus muscles. Symmetry of the corticomotor input to the plantarflexors was calculated for each participant as the paretic soleus MEP_{100} divided by the nonparetic soleus MEP_{100}. For both measures of symmetry, a value of 1.0 indicates perfect symmetry, with the paretic and nonparetic values being equal in magnitude; a value greater than 1 indicates the paretic was greater than the nonparetic; a value less than 1.0 indicates the paretic was less than the nonparetic.[139]

Two-way repeated measures analysis of variance (ANOVA) tests were used to test if MEP amplitude and plantarflexion ankle moment differed between limbs (paretic and nonparetic) and between pre to post testing for each session. For all significant interactions, post-hoc testing using a Bonferroni method was performed. If interactions were not significant, main effects were tested.

Changes in corticomotor symmetry and changes in plantarflexion ankle moment symmetry between conditions were tested using a paired *t*-test. For all significant differences in change in corticomotor or ankle moment symmetry, interlimb contributions to symmetry differences were tested. For interlimb change testing, two-way repeated measures ANOVA tests were also used to test if *change* in MEP amplitude and/or *change* in plantarflexion ankle moment differed between

sessions (FESW and NoFESW) and between limbs. Post-hoc testing using a Bonferroni method was performed for all significant interactions. If interactions were not significant, main effects were tested.

The relationship between change in corticomotor symmetry and change in plantarflexion ankle moment symmetry was tested for each session using a Pearson product-moment correlation coefficient. Relationships of paretic and nonparetic MEP amplitudes versus paretic and nonparetic plantarflexion ankle moments were also tested. All analyses were performed using SPSS version 23. An alpha level was set *a priori* at .05.

Results

Complete data sets were obtained from 19 participants. One participant could not return for the second session of NoFESW due to travel accommodations and was discarded from analysis. Optimal coil positions were measured for each group and were similar between sessions. Coil locations used for testing were on average 1.6±1.0cm anterior and 2.1±1.1cm lateral to the vertex of the skull and were not different between limbs (anterior, p=.36; lateral p=.28) or between sessions (anterior, p=.63; lateral, p=.59).

An example of MEP amplitude responses to FESW in the paretic and nonparetic limb of a single subject who showed a positive change in ankle moment symmetry is shown in Figure 5-2. For MEP amplitude measures, no significant limb

(paretic and nonparetic) by time (pre and post) interaction was observed following the FESW session ($F_{1,18}$=2.28, p=.14) or the NoFESW session ($F_{1,18}$=3.90, p=.06) (Figure 5-3A and B). There were significant main effects for limb ($F_{1,18}$=14.27, p<.01) and time ($F_{1,18}$=4.89, p=.04) following the FESW session and a main effect of limb ($F_{1,18}$=11.81, p<.01) but not time ($F_{1,18}$=0.97, p=.34) following the NoFESW session. For ankle moment measures, no significant limb by time interaction was observed following the FESW session ($F_{1,18}$=2.25, p=.15), but significant main effects were observed for limb ($F_{1,18}$=12.04, p<.01) and time ($F_{1,18}$=5.76, p=.02) (Figure 5-3C). There was a significant limb by time interaction following the NoFESW session ($F_{1,18}$=5.63, p=.02) for the ankle moment measure (Figure 5-3D). However, post-hoc testing revealed no significant pre to posttest difference for paretic ankle moment (p=.15) and a trend towards increase in nonparetic ankle moment from pre to post testing (p=.07).

Changes in corticomotor symmetry (p<.01) and plantarflexion ankle moment symmetry (p<.01) were significantly greater with FESW than NoFESW (Figure 5-4A and C). When testing inter-limb contributions of change in ankle moment symmetry, there was a significant limb by session interaction for change in plantarflexion ankle moment ($F_{1,18}$=10.72) (p<.01) (Figure 5-4D). Change in paretic ankle moment was significantly greater with FESW than NoFESW (p<.01) and different than change in nonparetic ankle moment for the FESW condition (p=.04) and the NoFESW session (p=.02). Change in nonparetic ankle moment was not different between sessions

(p=.68). When testing interlimb contributions of corticomotor symmetry, we also observed a significant limb by session interaction ($F_{1,18}$=7.12) (p=.02) (Figure 5-4B). Similar to ankle moment, change in paretic MEP amplitude was significantly greater with FESW than NoFESW (p<.01) and different from change in nonparetic MEP amplitude for the FESW (p=.04) and NoFESW (p=.02) conditions. Change in nonparetic MEP amplitude was not different between sessions (p=.20) (Figure5-4B).

There was a significant positive relationship between change in plantarflexion corticomotor symmetry and change in plantarflexion ankle moment symmetry in response to FESW (r(19)=0.64, p<.01) but not NoFESW (r(19)=-0.31, p=.20) (Figure 5-5). Interlimb correlation analysis of paretic and nonparetic symmetry components following FESW revealed a positive relationship between change in paretic plantarflexor MEP amplitude and change in paretic ankle moment (r(19)=0.62, p<.01) and no relationship between change in nonparetic plantarflexor MEP amplitude and change in nonparetic ankle moment (r(19)=0.27, p=.24) (Figure 5-6).

Discussion

Results of this study support the use of FES targeting plantarflexor muscles during gait training to improve corticomotor symmetry between limbs and ankle moment symmetry during walking in chronic stroke survivors. Additionally, this study provides novel evidence that improvements in corticomotor input to the paretic plantarflexors may drive increases in paretic plantarflexion ankle moment in response to a single session of gait training with FES in individuals with chronic stroke. This

suggests that rehabilitation strategies that effectively target corticomotor function of the lower limb could improve biomechanical walking function in chronic stroke survivors.

The relationships between change in plantarflexor corticomotor symmetry and change in plantarflexion ankle moment symmetry in response to FES offer novel insight into the neurophysiologic mechanisms underlying changes in post-stroke lower extremity biomechanical function that can be achieved during a single session of rehabilitation. FES-induced cortical plasticity has been reported in the upper extremity related to post-stroke motor function,[61-63] in the paretic lower extremity in response to prolonged dorsiflexion-targeted interventions[90] and in neurologically-intact individuals within a single session.[92,94,189] However, to our knowledge, there have been no previous studies that have investigated FES-induced cortical plasticity in response to a single session of rehabilitation in stroke survivors, and particularly how such cortical responses relate to changes in walking mechanics. Previous findings in both upper extremity[91] and lower extremity[92,189] have indicated that the coupling of volitional motor activity with electrical stimulation can achieve increases in corticomotor drive to the contracting muscle that last for at least 30 minutes if electrical stimulation delivery is rhythmic and coordinated with the targeted movement.[190] Similar findings have not been found after passive stimulation paradigms[91,92] and after walking without stimulation.[102] This evidence provided a basis and for the structuring and timing of the FES gait training session used in the present

study and support the environment offered by this training session as having the potential to promote similar cortical neuroplastic changes in the lower limb of stroke survivors. In environments where FES is coupled with volitional motor contraction during a functional task in stroke survivors, neuroimaging studies have consistently demonstrated shifts in the balance of cortical activation towards the contralateral lesioned primary motor and sensorimotor cortices and away from the same areas in the ipsilateral nonlesioned hemisphere.[61,62] Shifts in cortical balance of activity towards sensorimotor areas of the lesioned hemisphere were also found to be associated with improvements in upper extremity motor function.[61,62] Similarly, in the present study, we observed improvements in the balance of corticomotor input to the paretic and nonparetic plantarflexors following FES gait training that were related to improvements in ankle moment gait asymmetries between limbs (Figure 5-5). These improvements in corticomotor symmetry were driven by strengthened corticomotor drive to the paretic limb, as seen in Figure 5-4. Following FESW, there was a significant increase in paretic MEP amplitude and a related increase in paretic ankle moment (Figure 5-6). The observed increase in corticomotor drive to the paretic limb following FESW could be a result of increased cortical activity in the lesioned primary motor and somatosensory regions and selectively increased coupling between neuronal activity in lower extremity regions of primary motor and somatosensory cortices found in previous neuroimaging studies following FES therapy.[61-63,94] Further, these findings demonstrate that cortical neuroplastic changes can occur in plantarflexor muscles in the lower extremity despite receiving less cortical input than dorsiflexors,[5,7] that these

cortical changes are tied to improvements in walking patterns, and that neuroplastic changes can be made in response to a single session of FES gait training in individuals in the chronic stage of stroke.

In response to FESW, the MEP amplitude showed a main effect of time for both the paretic and nonparetic limb (Figure 5-3A). Increases in paretic limb MEP amplitude were greater than increases in nonparetic MEP amplitude (Figure 5-4B), but there was a small observed increase in nonparetic MEP amplitude mean. As observed in Figure 5-5, change in nonparetic corticomotor drive was variable between individuals. Though unrelated to change in nonparetic ankle moment, we observed an increase in corticomotor drive to the nonparetic plantarflexors in a few participants following gait training with FES that had not been reported in previous literature. Following FES to the paretic arm and hand muscles, Hara et al[61] found that increased cortical activity was observed in the lesioned sensorimotor cortex *relative to* the nonlesioned sensorimotor cortex. Consistent with these findings, the results of the present study showed that increased corticomotor symmetry following FES was a result of improved corticomotor drive to the paretic leg relative to that of the nonparetic leg (Figure5-4B). Thus, increased corticomotor drive in the nonparetic limb in some individuals does not contradict past reports and could further be explained by differences in the functional FES motor tasks between studies. Unlike upper extremity motor task training,[61,62] or simple ankle pumping tasks in the seated position previously reported in FES literature,[92,94] in this study the nonparetic limb was

required to be continuously active during walking and tied to the antiphasic stepping patterns of the paretic limb. As such, the nonlesioned sensorimotor cortex likely remained continuously active during the walking sessions, which could have enhanced FES-induced synchronization between pre- and post-synaptic activation[87] resulting in neuroplastic changes in the nonlesioned hemisphere in addition to the lesioned hemisphere. Alternatively, because a greater increase in nonparetic corticomotor input was observed in response to walking without FES (Figure 5-3), the FES gait training session could have actually *reduced* the enhancement of corticomotor drive to the nonparetic leg that may occur during typical walking patterns over time in stroke survivors, possibly through transcallosal inhibition from the increased cortical excitability of the lesioned hemisphere.[112,113] Future studies investigating the effect of FES on interhemispheric interactions in stroke survivors could elucidate the mechanisms underlying observed changes in corticomotor drive to the paretic and nonparetic limbs in the present study.

Although both corticomotor and ankle moment symmetry showed overall increases in response to FESW, we observed high variability between individuals in response to this gait training session. As evident in Figures 5-5 and 5-6 showing individual participant changes, FESW was not an effective strategy for inducing neuroplastic or biomechanical changes in some individuals who showed no change or a negative change in corticomotor and ankle moment measures. These results are consistent with the variability in biomechanical response to a similar session of FES

gait training previously reported by our laboratory[191] and variable changes in cortical activity and perfusion induced by FES in the upper extremity.[61] Variability in response between individuals may also provide explanation for inconsistencies between previous studies investigating the effectiveness of FES gait training amongst a heterogeneous population of stroke survivors[10,11] and for small effect sizes in the present study and those reported by previous literature.[10,11] It is conceivable that the stroke survivors in the present study who showed a positive response to FESW may have possessed a neural substrate that was activated or strengthened in response to FES gait training.[26,87] Though baseline measures of corticomotor function have been shown to have poor prognostic ability for rehabilitation outcomes in the chronic stage of stroke,[26] these findings suggest the potential for individual corticomotor response to a single session of rehabilitation to be an important indicator for response to a long-term intervention, similar to findings in the upper extremity.[26] Future research in the lower extremity could reveal that individuals who showed positive responses to the first session of a specific targeted rehabilitation strategy will show the greatest improvements in functional outcomes following a long-term intervention utilizing that strategy. Likewise, patients who showed no corticomotor response would benefit from utilization of other strategies to maximize gains in walking function. In this way, measurements of corticomotor response to a single session could provide a clinical tool to quantify individual neuroplastic responses to rehabilitation strategies that could ultimately help to individualize post-stroke rehabilitation amongst a heterogeneous stroke patient population and maximize post-stroke walking function.

Interestingly, in this study we observed that a session of walking without FES magnified corticomotor and ankle moment *asymmetries* during gait in the group overall (Figure 5-4A and C). Decreased corticomotor symmetry was primarily a result of enhanced nonparetic limb corticomotor drive, with a smaller contribution of suppressed paretic limb corticomotor drive, as shown in Figure5-4B. Decreased ankle moment symmetry following NoFESW was a result of both small decreases in ankle moment of the paretic limb and increases ankle moment of the nonparetic limb (Figure 5-5D). These results may suggest that typical asymmetrical walking patterns adopted by individuals post-stroke may induce neurophysiologic mechanisms that strengthen corticomotor imbalances between hemispheres and could potentially amplify gait asymmetries in some individuals. Gait training with FESW used in the present study may have induced neural mechanisms to interfere with these patterns in those same individuals, both enhancing corticomotor drive to the paretic leg and *reducing* the enhancement of corticomotor drive to the nonparetic leg following typical gait, as posited above. The lack of relationship between change in corticomotor symmetry and change in ankle moment symmetry in response to NoFESW (Figure 5-5) may be because, in the absence of a specific learning strategy, individuals adopted different biomechanical strategies (i.e. increased nonparetic trailing limb angle to increase propulsion)[165] during walking over time to achieve the same speeds. Thus, the relationship between change in corticomotor measures and change in biomechanical gait patterns may only exist when induced by specific targeted interventions that activate specific neural pathways.[94]

Limitations

Some limitations of the present study are important to consider in the interpretation of the results. Though fatigue could have influenced corticomotor measures of the present study, we think this is unlikely. Fatigue is characterized by a decline in force generation,[192] while in the present study increased ankle moments that were related to increased MEP responses with the paretic and nonparetic soleus muscles suggest that plantarflexor muscles were not fatigued. We did not stratify individuals for lesion size and location, which could have influenced corticospinal tract integrity and the potential to increase corticomotor excitability to the paretic limb. Though no differences were detected within or between sessions, quantification of pre-stimulus EMG activity showed differences between the paretic and nonparetic soleus muscle activity; individuals with the most severe motor impairments had difficulty modulating EMG activity at low levels and produced lesser raw EMG activity and greater normalized EMG activity in their paretic limb (see Appendix A, Figure A 5.1). This could have potentially increased differences between paretic and nonparetic MEP amplitudes, though would not have affected differences within and between sessions.

Conclusions

Findings of this study advance our understanding of the effectiveness of FES gait training to induce cortical plasticity to plantarflexor muscles limiting post-stroke

walking function and demonstrate that neuroplastic changes in the lower extremity are detectible following a single session of rehabilitation. Further, results provide insight to mechanisms of cortical plasticity underlying biomechanical improvements that can be made within a single session of rehabilitation in chronic stroke survivors. Findings from this study may provide a basis for future studies to test if measures of early corticomotor responses to a specific rehabilitation strategy provide a good predictor of the potential for gains in functional walking ability. Future research may lead to the development of effective and individualized rehabilitation strategies that may interrupt learned corticomotor imbalances underlying post-stroke walking dysfunction and maximize walking ability in stroke survivors.

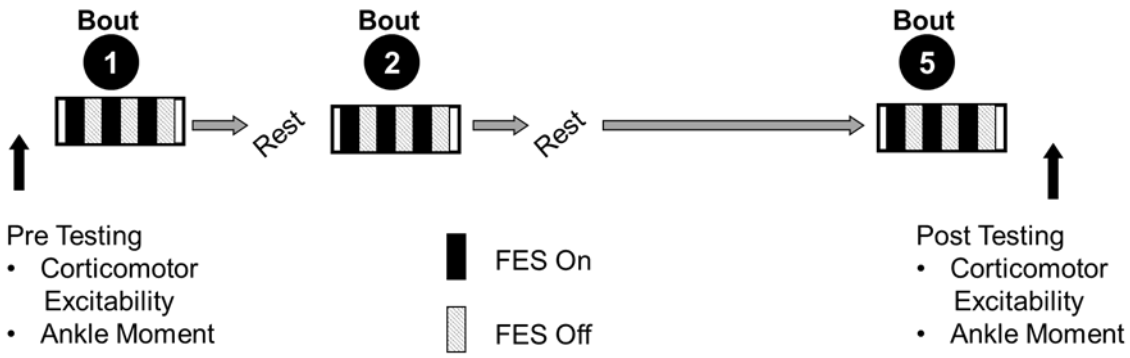

Figure 5-1. Schematic of FES gait training session. FES: Functional Electrical Stimulation

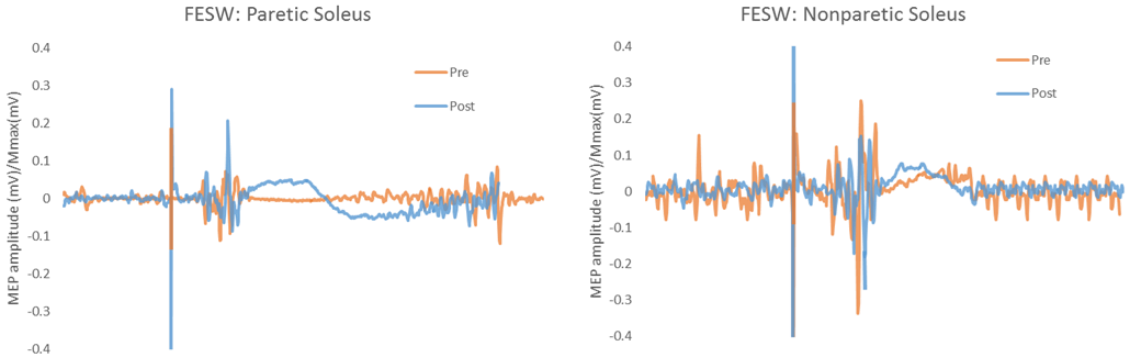

Figure 5-2. Example raw MEP_{100} data from a participant's paretic (top) and nonparetic (bottom) soleus muscles showing a positive change in corticomotor symmetry in response to FESW. FESW: walking session with functional electrical stimulation

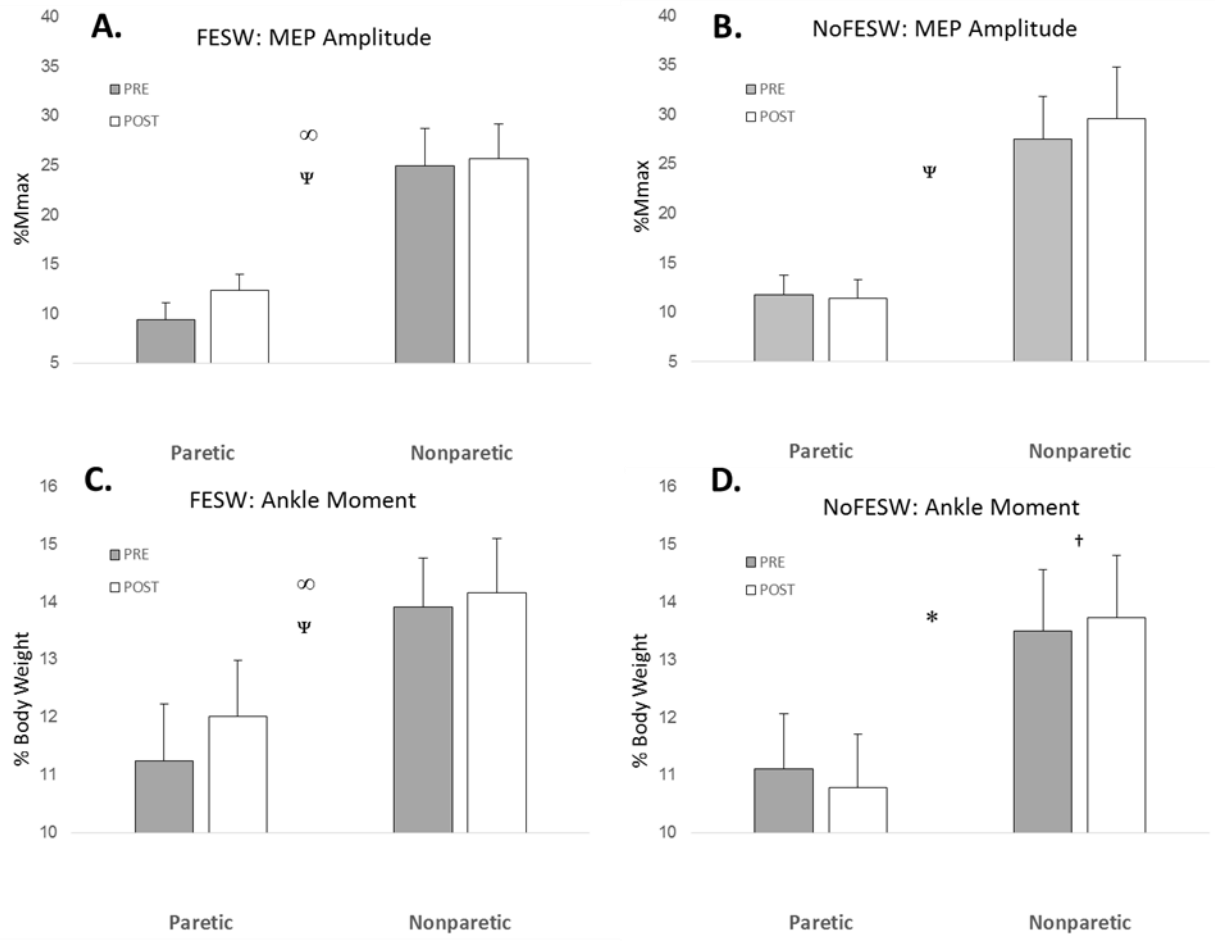

*Figure 5-3. MEP amplitude and plantarflexion ankle moment (mean±SE) for the paretic and nonparetic limbs during pre- and post testing for the FESW (A and C) and NoFESW (B and D) sessions. * indicates significant interaction. ∞ indicates a main effect of time (pre and post). Ψ indicates a main effect of limb. † indicates trend towards pre to post difference in the nonparetic limb with p=.07. Significance reported at the p<.05 level. FESW: walking session with functional electrical stimulation; NoFESW: walking session without functional electrical stimulation.*

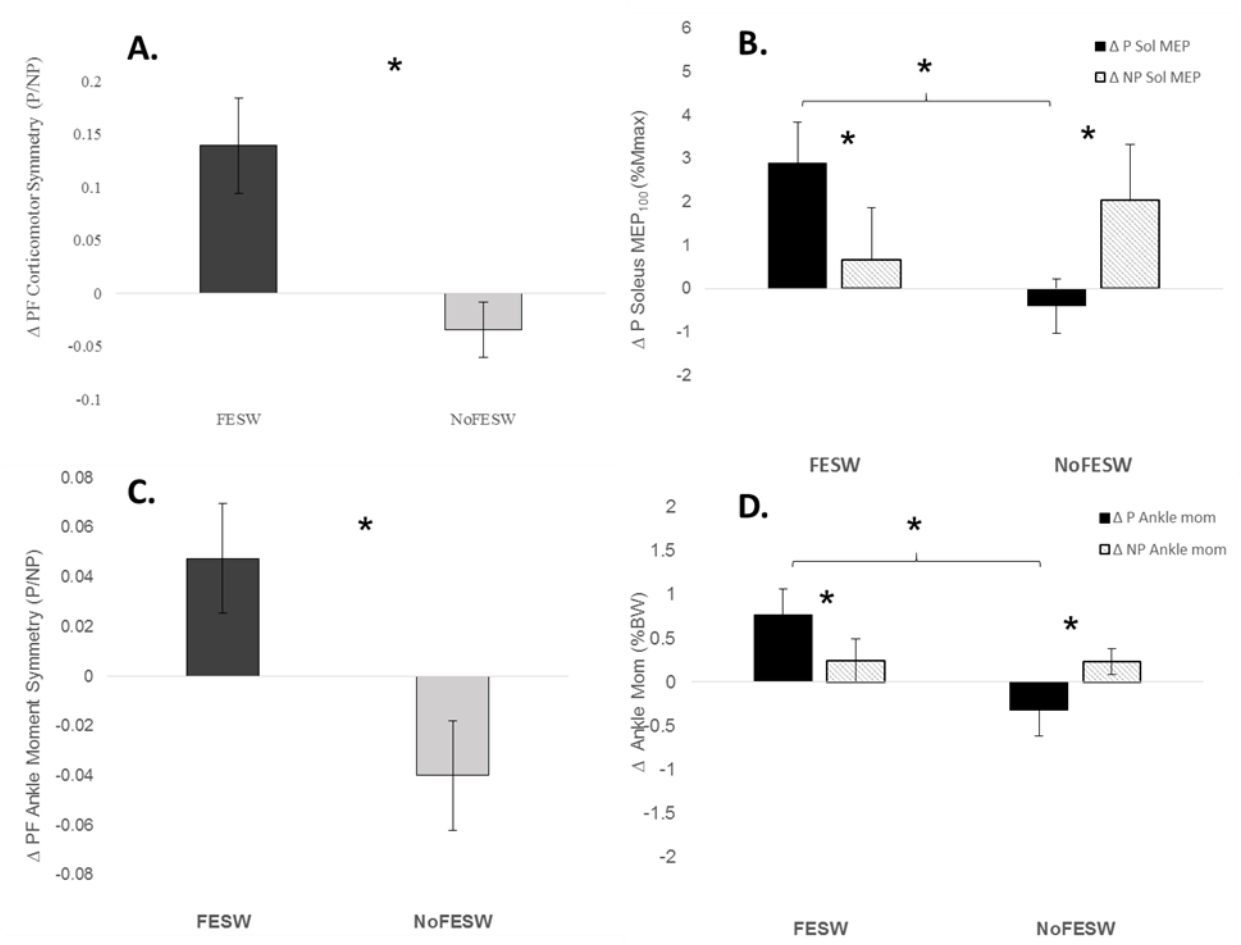

*Figure 5-4. Changes (mean±1SE) in plantarflexor corticomotor symmetry (A) and changes (mean±1SE) in plantarflexion ankle moment symmetry (C) in response to FESW and NoFESW. Paretic and nonparetic limb change components of change in plantarflexor corticomotor symmetry (B) and change in plantarflexor ankle moment symmetry (D) are shown. Significant limb by session interactions were observed for both changes in MEP amplitude (B) and changes in plantarflexion ankle moment (D). * Indicates significant difference for post hoc comparisons at the p<.05 level. P: paretic; NP: nonparetic; Ankle mom: Ankle moment; PF: plantarflexor; Sol: soleus muscle; FESW: walking session with functional electrical stimulation; NoFESW: walking session without functional electrical stimulation.*

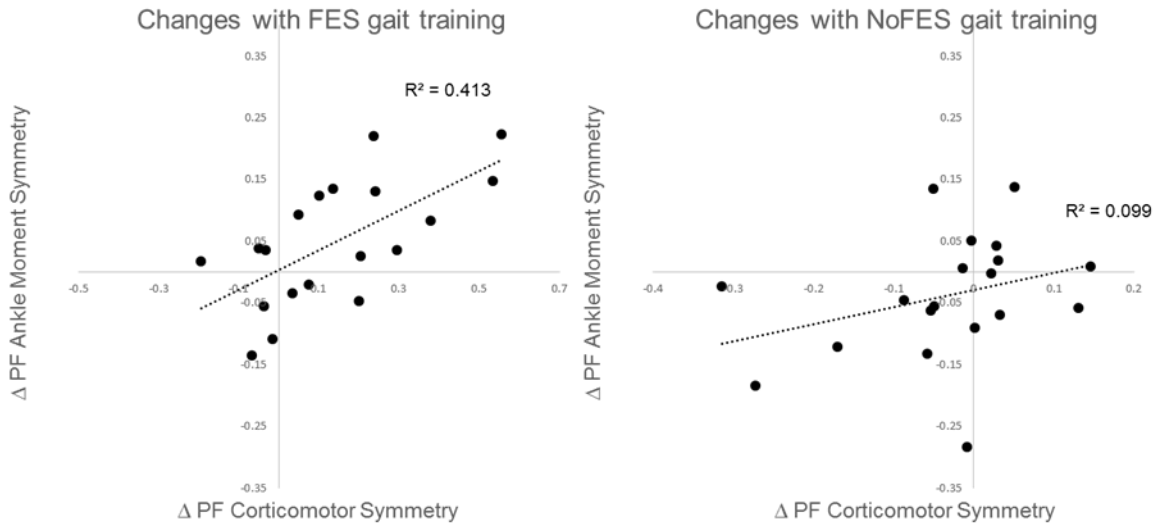

Figure 5-5. There was a positive relationship between Δ PF corticomotor symmetry and ΔPF ankle moment symmetry with FES gait training (left) (r(19)=0.64, p<0.01). In response to gait training without FES, no relationship was observed (right) (r(19)=-0.31, p=.20). PF: plantarflexor; FESW: with functional electrical stimulation; NoFESW: without functional electrical stimulation.

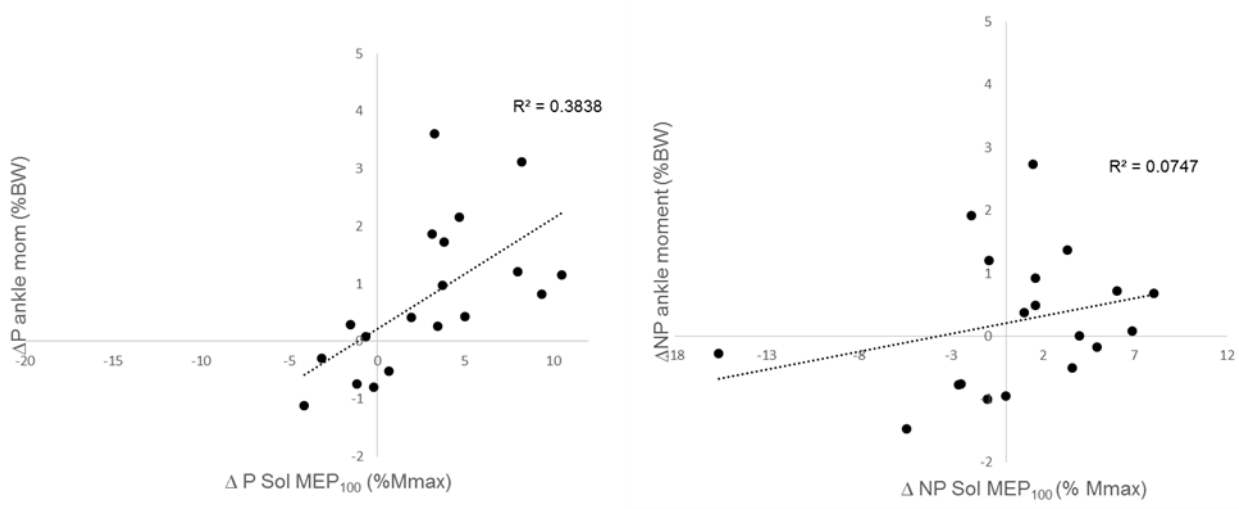

Figure 5-6. There was a positive relationship between Δ paretic MEP_{100} and Δ paretic ankle moment with FES gait training (left) (r(19)=0.62, p<0.01). No relationship was observed between Δ nonparetic MEP_{100} and Δ nonparetic ankle moment (right) (r(19)=0.27, p=.24). P: paretic; NP: nonparetic; Sol: soleus muscle

Chapter 6

CONCLUSIONS

The main goal of this dissertation has been to investigate corticomotor characteristics that influence post-stroke clinical walking function and biomechanical gait impairments and to determine the effects of a single session of rehabilitation on lower extremity corticomotor excitability in chronic stroke survivors. In the following sections, the specific aims and hypotheses will be reviewed and findings will be summarized.

Aim 1 Findings:

Balance of corticomotor drive to the paretic and nonparetic upper extremity has been shown to be related to the level of motor recovery in the upper extremity and is influenced by muscle activation. In addition to reduced corticomotor drive to the paretic arm and hand, overly-active corticomotor drive to the nonparetic arm and hand muscles has been related to poor motor recovery. **Aim 1 of this dissertation was to compare corticomotor input to the lower extremity in individuals with chronic stroke who demonstrate good versus poor recovery of walking function and neurologically-intact controls.**

H1.1. Corticomotor symmetry between paretic and nonparetic lower extremity muscles will be different in individuals with poor versus good post-stroke walking recovery and neurologically-intact controls.

H1.1.1. Corticomotor symmetry will be different in resting versus active motor states in individuals will poor versus good walking recovery following stroke.

H1.1.2. Atypical patterns of corticomotor input will be greater in plantarflexors than dorsiflexors in individuals with poor versus good walking recovery following stroke.

Corticomotor symmetry to both plantar and dorsiflexor muscles was lesser in stroke survivors with poor versus good walking recovery, regardless of active or resting condition. In individuals with poor post-stroke walking recovery, corticomotor symmetry of both muscles resulted from decreased paretic *and* increased nonparetic limb corticomotor excitability when compared to neurologically-intact controls. During rest, similar levels of corticomotor symmetry were observed in plantarflexors and dorsiflexors in stroke survivors; however, during an active motor state corticomotor symmetry to dorsiflexor muscles improved in stroke survivors when compared to the resting state, while there was no change in plantarflexor muscles. This suggests that lower limb muscles of stroke survivors may be affected by similar atypical interhemispheric mechanisms that have been observed during active motor states in the upper extremity and that plantarflexors may be more affected by these mechanisms than dorsiflexors. Additionally, stroke survivors with poor walking recovery seem to be affected to a greater degree by mechanisms contributing to corticomotor symmetry than individuals with good walking recovery.

H1.2. During activation of the nonparetic lower limb, there will be altered corticomotor drive to the paretic lower limb muscles in stroke survivors with poor versus good walking recovery.

During nonparetic limb dorsiflexion contraction, stroke survivors with poor walking recovery showed enhanced corticomotor drive to the paretic TA muscle compared to during rest or paretic dorsiflexion contraction. This was not observed in individuals with good walking recovery. These results suggest that stroke survivors with poor walking recovery may rely on contraction of the nonparetic limb muscles and activation of the nonlesioned hemisphere to increase corticomotor drive to the paretic TA muscle.

For simplicity of manuscript publication, we did not report the results for this analysis from the paretic soleus muscle in Chapter 3. We did not observe a similar atypical pattern in the paretic soleus muscle during the nonparetic plantarflexion contraction condition as we did in the paretic TA muscle; all participants in both fast and slow walking groups showed the greatest corticomotor drive to the paretic soleus during the paretic plantarflexion contraction. The different effect of nonparetic lower limb contraction on corticomotor drive between dorsi- versus plantarflexors may be a result of differences in the control of the corticomotor pathways between these two muscles.

Aim 2 Findings:

Impairments in both neurological and biomechanical function have been shown to limit walking ability in chronic stroke survivors. However, a disconnect exists in our understanding of salient neurophysiologic contributions to biomechanical

walking function following neurologic insult. **Aim 2 of this dissertation was to determine the influence of corticomotor drive to the lower extremity on biomechanical strategies used to achieve an individual's level of walking function in the chronic stage of stroke.**

H2.1. There will be a positive relationship between plantarflexor corticomotor symmetry and changes in plantarflexion ankle moment symmetry with changes in walking speed in individuals with chronic stroke.

As hypothesized, there was a positive relationship between plantarflexor corticomotor symmetry and change in plantarflexion ankle moment symmetry when stroke survivors increased walking speed from their self-selected to fastest speeds.

H2.2. Corticomotor symmetry to plantarflexor muscles will moderate the relationship between change in plantarflexion ankle moment symmetry and walking speed modulation in individuals with chronic stroke.

In this analysis, we observed an interaction between plantarflexor corticomotor symmetry and change in ankle moment when predicting degree of gait speed modulation in individuals post-stroke. Individuals with the greatest corticomotor symmetry between limbs increased their walking speed by improving the ankle moment contribution of the paretic leg, reducing ankle moment asymmetries between limbs. In contrast, individuals with the least corticomotor symmetry increased their walking speed by increasing reliance on the ankle moment contribution of the nonparetic leg, magnifying their gait asymmetries.

H2.3. Corticomotor drive to the paretic tibialis anterior will be related to dorsiflexion angle during gait in individuals with chronic stroke.

We did not observe a relationship between paretic TA MEP amplitude and ankle dorsiflexion angle in stroke survivors during either the paretic or nonparetic dorsiflexion contraction. For simplicity, within the published manuscript we chose to report only the plantarflexor components of walking (see Chapter 4). However, we have reported these relationships regarding dorsiflexion below (Figure 6-1 and 6-2). The lack of relationship between paretic dorsiflexor corticomotor excitability and paretic ankle angle during walking could be explained by the lack of association between dorsiflexion and post-stroke walking function.[129] Though we found that atypical corticomotor drive to the paretic TA was associated with level of walking function in stroke survivors (Chapter 3), individuals with poor paretic dorsiflexion angle did not necessarily walk at slower gait speeds. Paretic limb clearance may be achieved using biomechanical strategies other than dorsiflexion through TA muscle activation; individuals may adopt strategies such as increased hip or knee flexion angles for paretic limb clearance during swing.[130] Thus, it is possible that dorsiflexion ankle angle measures may not capture potential gait impairments that influence level of post-stroke walking function.[129] Future research could investigate potential cortical interactions between dorsi- and planterflexor motor cortical representations during muscle contraction that may be related to key biomechanical determinants of post-stroke walking function, such as propulsion.[9,140]

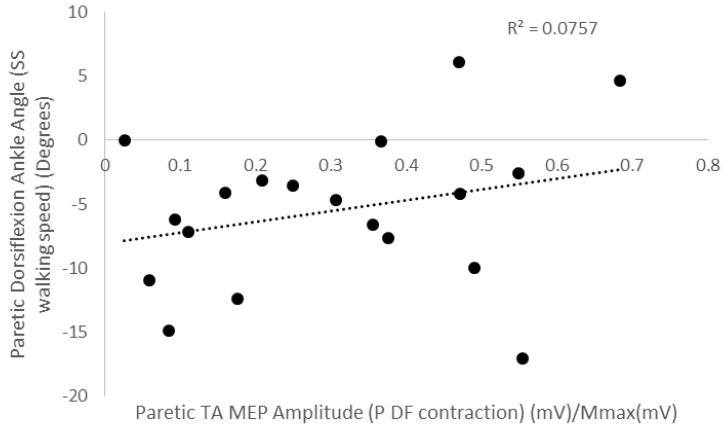

Figure 6-1. There was no relationship between paretic TA MEP_{100} amplitude during paretic (P) dorsiflexion (DF) contraction (methods described in Chapter 3) and paretic dorsiflexion angle at self-selected walking speed and calculated during the swing phase of gait (r(19)=0.28, p=.25). P: paretic; SS: self-selected; DF: dorsiflexion

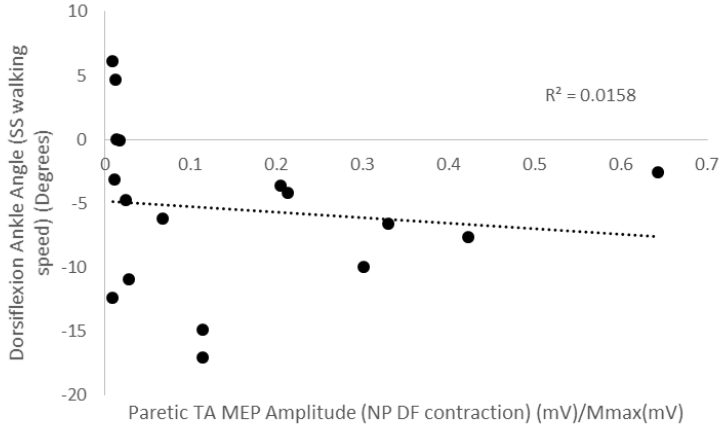

Figure 6-2. There was no relationship between paretic TA MEP_{100} amplitude during nonparetic (NP) dorsiflexion (DF) contraction (methods described in Chapter 3) and paretic dorsiflexion angle at self-selected walking speed and calculated during the swing phase of gait (r(17)=0.13, p=.62). NP: nonparetic; SS: self-selected; DF: dorsiflexion

Aim 3 Findings:

When key gait impairments, namely paretic limb propulsion, are targeted effectively, FES gait training can produce robust improvements in walking function in individuals with chronic stroke.[77] FES-induced cortical plasticity has been demonstrated following long-term upper limb training in patients with chronic stroke and following single-session lower limb training in neurologically-intact individuals. However, it is unknown if cortical changes can be made in response to a single session of FES training in individuals post-stroke and if potential changes could be related to short-term changes biomechanical walking function. **Aim 3 of this dissertation was to determine the relationships between changes in corticomotor excitability to the lower extremity muscles and changes in walking biomechanics in response to a single session of gait rehabilitation using functional electrical stimulation in individuals with chronic stroke.**

H3.1. Improvements in corticomotor symmetry to the plantarflexor muscles and plantarflexor ankle moment symmetry will be greater following a single session of gait training with FES than following a single session of gait training without FES.

Individuals showed greater improvements in plantarflexor corticomotor symmetry and ankle moment symmetry following gait training with FES than without FES. Improvements in corticomotor and ankle moment symmetry were driven by an increase in paretic corticomotor excitability and paretic ankle moment. Interestingly, both corticomotor symmetry and ankle moment symmetry decreased following a session of gait training without FES. These changes were driven by both increased nonparetic corticomotor excitability and nonparetic ankle moment and decreased

paretic corticomotor excitability and paretic ankle moment. These findings suggest that stroke survivors may reinforce cortical imbalances and asymmetrical gait patterns during their typical ambulation strategies. Walking with FES may disrupt these neurophysiologic and biomechanical reinforcements and promote balanced cortical activity and biomechanical walking patterns.

H3.2. Changes in corticomotor drive to plantarflexor muscles will be related to changes in ankle moment during walking following gait training with FES in stroke survivors.

As predicted, participants who improved corticomotor symmetry to paretic and nonparetic plantarflexors showed related improvements in ankle moment symmetry in response to walking with FES. This relationship was driven by neurophysiologic and biomechanical changes in the paretic limb, as we observed a related change in corticomotor drive to paretic plantarflexors and change in paretic ankle moment. These findings provide novel evidence of short-term changes in corticomotor function that may underlie positive changes in biomechanical walking function in individuals with chronic stroke.

H3.3. A session of gait training with FES will reduce atypical corticomotor drive to the paretic dorsiflexors during paretic and nonparetic dorsiflexion contraction in stroke survivors.

H3.3.1. Changes in atypical corticomotor drive to paretic dorsiflexors during paretic dorsiflexion contraction will be positively related to changes in paretic dorsiflexion ankle angle during walking following gait training with FES.

H3.3.2. Changes in atypical corticomotor drive to paretic dorsiflexors during nonparetic dorsiflexion contraction will be negatively related to changes in paretic dorsiflexion ankle angle during walking following gait training with FES.

For this dissertation project we chose to focus on plantarflexor neurophysiologic and biomechanical characteristics for a few reasons: 1) results from aim 1 (Chapter 2) indicate that corticomotor drive to plantarflexors is more impaired than that of dorsiflexors, 2) results from aim 2 indicated that plantarflexor corticomotor excitability influences critical biomechanical factors to post-stroke walking speed (Chapter 4) while no relationships were observed in dorsiflexors (Figure 6-1 and 6-2) and 3) biomechanical factors driven, in part, by plantarflexor muscles have been consistently shown to be the most significant limiters of post-stroke walking speed.[78,130,140] However, we were interested in testing the effects of a session of gait training with FES and without FES on the interesting atypical corticomotor patterns observed in the paretic TA during nonparetic TA contraction from Aim 1 (Chapter 3). These data are presented in Figure 6-3. No significant

interactions were detected between conditions of limb contraction (paretic or nonparetic contraction) and time (pre and post-testing) for paretic TA corticomotor excitability in response to either session. The lack of a significant findings may be due to the fact that participants participating in the FES training were a combined population of fast and slow walkers who possessed different baseline corticomotor patterns within their paretic TA during muscle contraction (see Chapter 3). Additionally, we observed no changes in paretic ankle angle during swing following either session (FESW, p=.13; NoFESW, p=.16); for this reason we did not test relationships between change in TA corticomotor excitability and changes in ankle angle following gait training with FES. Future research could determine if similar findings exist in subject samples dichotomized based on baseline neurophysiologic measures.

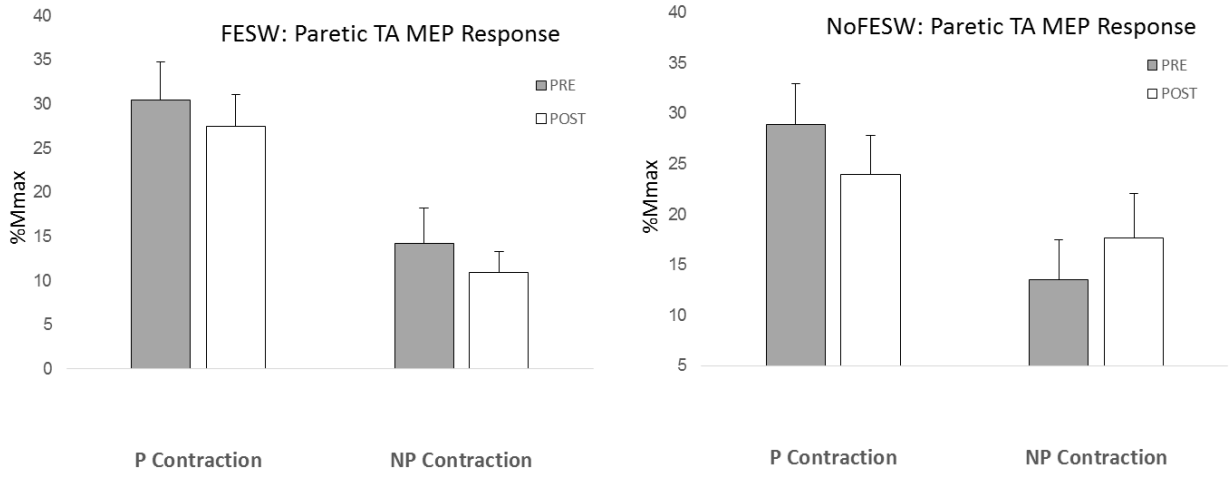

Figure 6-3. Paretic MEP amplitude responses to FESW (left) and NoFESW (right). No significant interactions were detected between contracted limb (paretic or nonparetic) and time (pre and post-testing) for paretic TA corticomotor excitability following the FESW ($F_{1,17}$=1.27, p=.28) and NoFESW session ($F_{1,17}$=3.59, p=.07). However, a trend may be observed during the nonparetic conctraction condition; atypical corticomotor drive to the paretic TA during NP dorsiflexion contraction may be reduced following FESW, while it may show enhancement following NoFESW. All paretic TA MEP data were collected using identical methods to those described in Chapter 3. P: paretic; NP: nonparetic; FESW: with functional electrical stimulation; NoFESW: without functional electrical stimulation.

Future Directions

Finding from this dissertation project have enhanced our current understanding of cortical mechanisms underlying walking function in individuals with chronic stroke. Our approach has afforded us insight into understanding the relationship between impairments in central nervous system function and the clinical manifestations of specific gait impairments that limit walking ability in stroke survivors. Additionally, findings have advanced our understanding of corticomotor responses to novel rehabilitation strategies that improve lower extremity motor function. However, findings from this project have raised important questions. First, although TMS methodology provides information about strength of corticomotor pathways to specific muscles, it alone cannot determine the specific neural origins that underlie measures of corticomotor excitability. Future studies could use advanced neuroimaging techniques to offer better spatial resolution of cortical activity in motor areas of interest. Additionally, neuroimaging may have the ability to detect corticomotor and interhemispheric pathways in individuals with absent motor evoked potential responses, another limitation of TMS approaches in severely impaired individuals. Additionally, future work could investigate whether lower extremity

corticomotor responses to a single session of rehabilitation, as observed in this study, could predict an individual's functional walking outcome in response to long-term interventions utilizing specific strategies. This project has provided a first step towards advancing evidence-based rehabilitation efforts in neurologic patient populations and could provide an objective basis on which we may begin to empower clinicians to implement effective rehabilitation strategies that optimize functional walking recovery in stroke survivors.

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Appendix A

PRE-STIMULUS EMG ACTIVITY

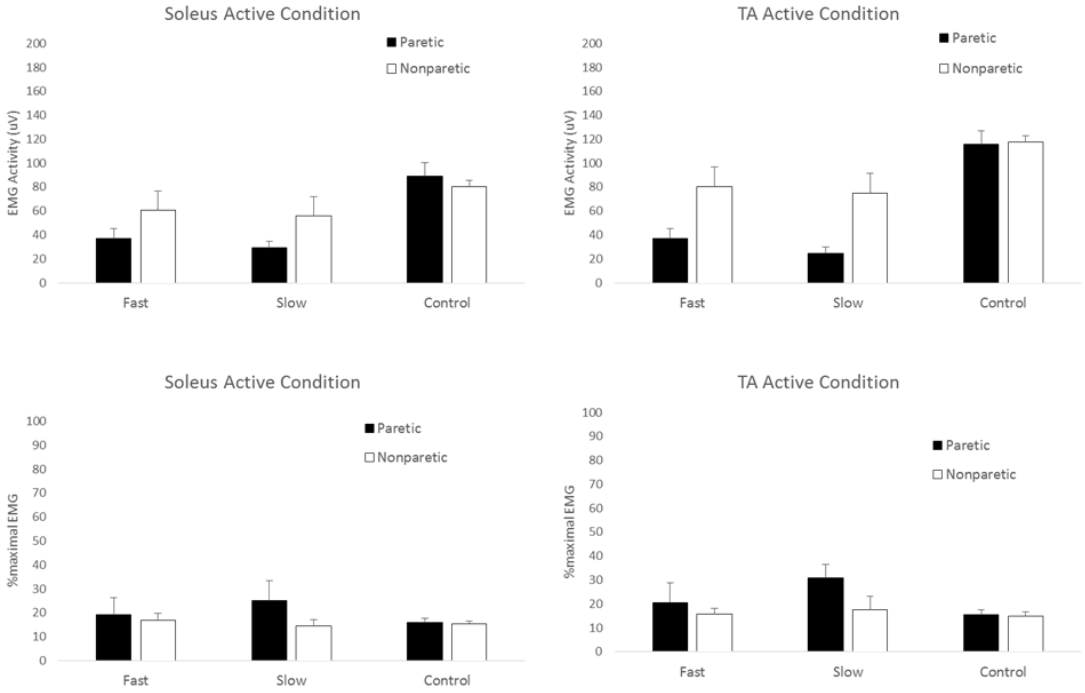

Figure A-1. Pre-stimulus EMG activity (mean±SE) for the paretic and nonparetic soleus (left) and TA (right) muscles in each group during the active condition. Values for all participants in the fast-stroke (n=16), slow-stroke (n=13) and neurologically-intact controls (n=14) are shown in raw microvolt units (top). Values for a select number of participants for whom EMG data was collected during MVIC in the fast-stroke (n=10), slow-stroke (n=8) and neurologically-intact controls (n=13) are shown normalized to the maximum EMG amplitude during maximum volitional isometric contraction (MVIC) (bottom). Though all participants were provided with biofeedback and asked to target a 15% MVIC level EMG during the active condition, maximum EMG amplitude during MVIC was not recorded for all participants in this study. Overall, the paretic limb of both stroke groups showed lower raw EMG activation levels (top) and greater % total volitional EMG levels than controls (bottom) due to activation deficits and impairments with volitional motor control. The nonparetic limbs of the stroke-groups also showed lower raw EMG activation levels than controls (top), but when normalized to EMG during MVIC, there were no differences in nonparetic limb EMG amplitudes between groups for either the soleus or TA muscle (bottom).

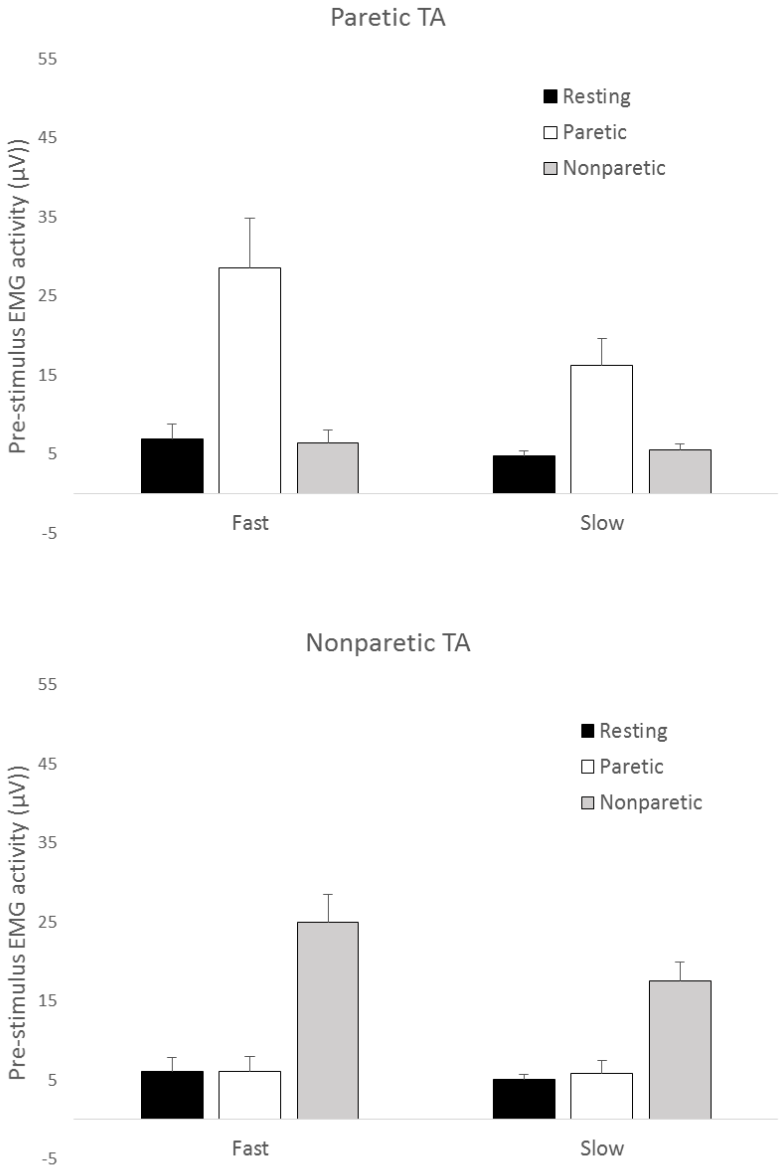

Figure A-2. Raw pre-stimulus EMG activity (mean±SE) for the paretic TA (top) and nonparetic TA (bottom) in fast and slow walker groups during each condition of contraction (resting, paretic, nonparetic). Groups showed similar activity in both muscles during the resting condition. Neither the paretic TA nor nonparetic TA showed an increase in activity during contraction of the contralateral TA. The paretic limb of the slow walkers showed lower raw EMG activity than the fast walkers.

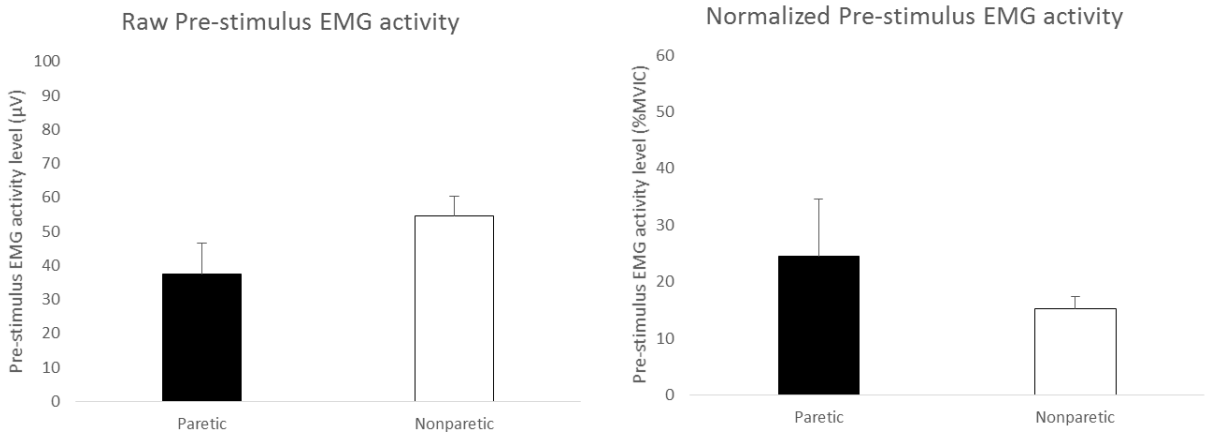

Figure A-3. Pre-stimulus EMG activity (mean±SE) for the paretic and nonparetic soleus for all trials used for analysis. Raw pre-stimulus values for all participants (n=23) (left). Values for a select number of participants (n=16) for whom EMG data were collected during MVIC are shown normalized to the EMG activity during maximal volitional plantarflexion contraction.

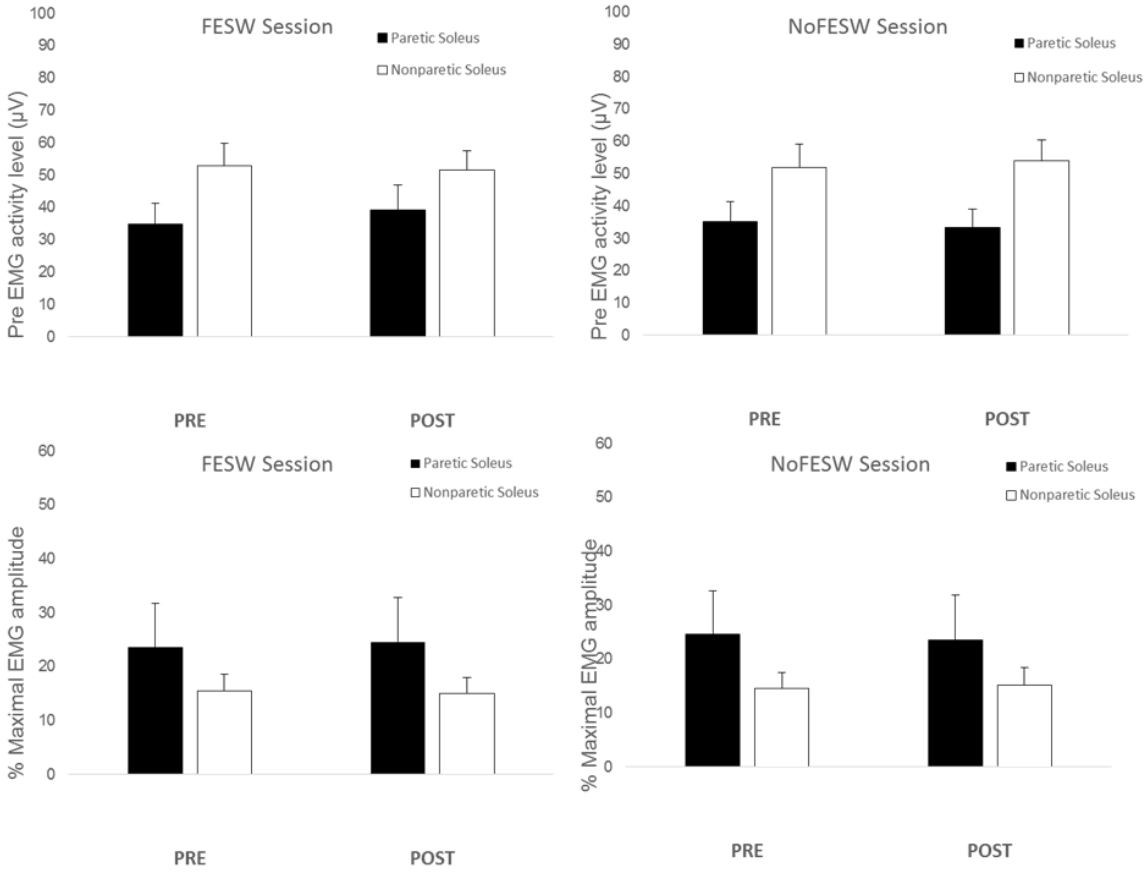

Figure A-4. Pre-stimulus EMG activity (mean±SE) for the paretic and nonparetic soleus muscles for the FESW (left) and NoFESW (right) session. Values for all participants included in analyses (n=19) are shown in raw microvolt units (top). Values for 16 participants are shown normalized to the maximum EMG amplitude during a maximum volitional isometric contraction (MVIC) (bottom). Overall, the paretic limb showed lower raw EMG activation levels (top) and greater % total volitional EMG levels than the nonparetic limb (bottom) due to activation deficits and impairments with volitional motor control in some subjects. FESW: with functional electrical stimulation; NoFESW: without functional electrical stimulation.

Appendix B

TMS MEASURE RELIABILITY IN PARTICIPANTS WITH STROKE

We collected within session reliability data for TMS measures for the paretic limb for the first twelve participants in Aim 1 to help determine the TMS measure of interest for this study. We chose to use the TA muscle in our reliability measures because TA MEPs were consistently more pronounced than soleus MEPs, particularly in the most impaired individuals.

Methods: Methods using to collect reliability data were identical to those described in Chapter 2. Briefly, the hotspot for the paretic TA was identified while the participant maintained a light dorsiflexion contraction at 15% of their maximal volitional paretic TA EMG activity (see Chapter 2 methods for details). Participants were provided real-time visual EMG biofeedback to assist them in maintaining a constant level of muscle activity at 15% of their EMG activity during a maximal volitional dorsiflexion contraction. A stimulus-response curve was produced from application of TMS pulses at a frequency of 0.2 Hz at intervals of 3% of the stimulator's output intensity from subthreshold through 100% maximum output intensity. These testing procedures were repeated to yield two stimulus-response curves for the paretic TA muscle. All MEP data were normalized to the maximal response to common peroneal nerve stimulation (Mmax).

Pre-stimulus EMG was quantified as previously described (see Chapter 2 methods) and paretic TA EMG activity was not different between the two trials (p=.67). All MEP data were analyzed as previously described (see Chapter 2

methods). MEP amplitude was quantified as the peak-to-peak value of the EMG response within a 100ms window duration beginning at 10ms post stimulus artifact. Normalized peak-to-peak amplitudes of the MEPs were plotted against the stimulator output intensity to form a stimulus-response curve (Figure B-1). A Levenberg-Marquardt algorithm was used to fit a modified Boltzmann equation to the data using the following equation:[135]

$$y = MEP_{min} + \frac{MEP_{max} - MEP_{min}}{1 + e^{m(I_{50} - x)}}$$

Parameters of minimum MEP (MEP_{min}), **maximum MEP ($\mathbf{MEP_{max}}$)**, **slope (*m*)**, and intensity at which the curve's slope was the steepest (**$\mathbf{I_{50}}$**) were derived from the equation. The **active motor threshold** (MT) was defined as the intensity of the curve at which the first derivative increased above 5% of its maximum.[137]A thorough description of each of these parameters can be found in Devanne et al.[135] Data were excluded if the stimulus-response curve did not have a R^2 value of greater than or equal to 0.75.[137] Three out of the twelve participants had poor stimulus-response curve fits not meeting these criteria and parameters derived from their stimulus-response curve were discarded from analysis. An average of three peak-to-peak MEP amplitudes of the paretic TA at 100% stimulator output intensity (**$\mathbf{MEP_{100}}$**) were taken for each condition.

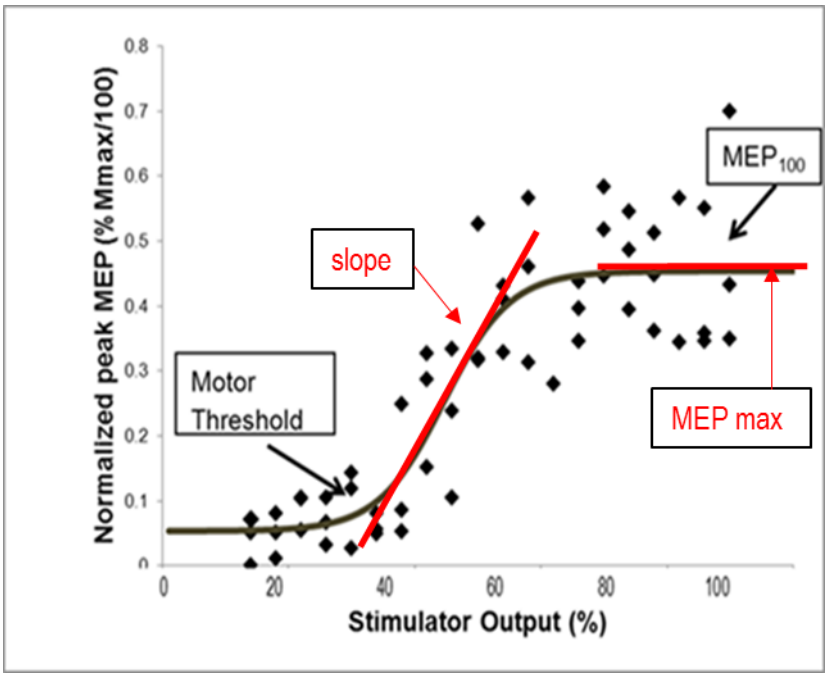

Figure B-1. Sample stimulus-response curve fitted to normalized MEP amplitude data. Motor threshold, slope, MEP maximum (MEP max) and MEP_{100} measures are identified.

Results:

TMS Measure	ICC(3,k)			
	Single Measure	95% CI	Average Measure	95%CI
Active Motor Threshold	.766	.326±.932	.867	.492±.965
Slope	.133	-.513±.651	.234	-2.107±.788
I_{50}	.716	.125±.929	.835	.223±.963
MEP maximum	.508	-.087±.838	.674	-.191±.912
MEP_{100}	.932	.926±.995	.962	.952±.997

Table B-1. ICCs for all TMS measures. The average MEP_{100} measure showed the greatest reliability within a session (n=12). Active motor threshold showed the greatest reliability of the parameters derived from the stimulus-response curve, but could not be calculated for all participants (n=9).

Appendix C

IRB APPROVAL LETTERS

RESEARCH OFFICE

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

DATE: May 17, 2012

TO: Jacqueline Palmer, graduate student
FROM: University of Delaware IRB

STUDY TITLE: [336375-1] CORTICAL MOTOR ORGANIZATION AND EXCITABILITY IN INDIVIDUALS WITH CHRONIC STROKE

SUBMISSION TYPE: New Project

ACTION: APPROVED
APPROVAL DATE: May 17, 2012
EXPIRATION DATE: May 15, 2013
REVIEW TYPE: Full Committee Review

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

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

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

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

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

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

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

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

RESEARCH OFFICE

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

DATE: April 23, 2014

TO: Jacqueline Palmer, DPT
FROM: University of Delaware IRB

STUDY TITLE: [594539-1] Brain responses to gait training with functional electrical stimulation in chronic stroke: a TMS study

SUBMISSION TYPE: New Project

ACTION: APPROVED
APPROVAL DATE: April 23, 2014
EXPIRATION DATE: April 15, 2015
REVIEW TYPE: Full Committee Review

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

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

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

Appendix D

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