DISSERTATION

NEUROMUSCULAR DYSFUNCTION:

CHARACTERIZATION AND REHABILITATION

Submitted by

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ABSTRACT

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Manifestation of action in the physical world is reliant on afferent signaling, processing, efferent signaling, and transduction of this signal into force production and control at the musculature. A variety of neural conditions compromise this chain between signal input and control of force and movement. The overall objective of the four investigations discussed herein is the enhanced characterization and treatment of three conditions leading to neuromuscular dysfunction: healthy aging, peripheral neuropathy, and stroke.

The population of the United States is “graying”. Among the array of health issues associated with aging, decline of muscle force production and control is of key import. Little information exists for the relationship of neuromuscular control about the ankle to postural control in the context of aging. Experiment #1 investigated the contribution of neuromuscular control about the ankle to postural steadiness in healthy subjects who were young, old, and very old. The most robust correlations between ankle force control, postural stability, and physical function were found in the very old subjects.

Peripheral neuropathy (PN) is a progressive condition in which neurons found beyond the central nervous system “die back”. An increase in peripheral neuropathy incidence is virtually inevitable considering the enhanced prevalence of diabetes and chemotherapeutic treatment of cancers, as well as the “graying” of the population of the

United States as advanced age contributes to PN (demonstrated by an enhanced incidence to approximately 15% in the population over forty years of age). Experiment #2 investigated the contribution of neuromuscular control about the ankle to postural steadiness in subjects with peripheral neuropathy as compared to young healthy and older healthy subjects. The most robust correlations force control and postural stability were found in the peripheral neuropathy patients.

Stroke is a leading cause of long-term adult disability in the United States which often leads to neuromuscular dysfunction of the upper limb. An element of great importance to survivors of stroke is quality of life in the face of neuromuscular dysfunction. A decreased capacity, or outright inability, to perform functional tasks such as light housework, cooking, bathing and dressing oneself is associated with an increased risk for depression and may necessitate enhanced care such as that found while living with family or in assisted-living communities. Conventional modes of stroke rehabilitation typically yield only modest improvements in upper extremity function. Stroke rehabilitation techniques must be enhanced to afford a greater quality of life to survivors of stroke.

Experiments #3 and #4 utilized repetitive transcranial magnetic stimulation as an experimental treatment for stroke rehabilitation. In Experiment #3, survivors of stroke were randomized to either daily repetitive transcranial magnetic stimulation immediately followed constraint induced therapy or an identical treatment in which sham stimulation was used in place of repetitive transcranial magnetic stimulation. The underlying logic of this investigation was that magnetic stimulation of the cortex would enhance neuroplasticity, thereby enhancing recovery. Though repetitive transcranial magnetic

stimulation was found to boost excitability at the level of the motor cortex as opposed to sham stimulation, few functional results were noted. Experiment #4 provided repetitive transcranial magnetic to two groups of stroke survivors, one of which triggered the stimulation by surface electromyogram activity at the first dorsal interosseous while the second group received transcranial magnetic stimulation passively. Results similar to those in Experiment #3 were noted in that the triggered stimulation proved to increase cortical excitability (and inhibition, in this case) as compared to passive stimulation while few differences in motor function were found.

The findings of these four studies improve the characterization of aging, peripheral neuropathy, and stroke. More importantly, these findings are likely to contribute to future treatments and rehabilitation techniques with the goal of improved neuromuscular function thereby improving quality of life.

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TABLE OF CONTENTS

CHAPTER I – MANUSCRIPT I

The relation of isometric ankle force control with postural stability and functional mobility in older adults

Summary

The purpose was to determine 1) the effect of advanced healthy aging on the variability of motor output in the ankle dorsiflexors and plantarflexors, and 2) the relation between ankle motor variability and postural stability in advanced healthy aging. Old older adults (N=25, O-OA) and young older adults (N=22, Y-OA) underwent assessment of postural stability during quiet standing, isometric strength (maximal voluntary contraction, MVC), and force steadiness (2.5% MVC) of the ankle dorsiflexor (DF) and plantarflexor (PF) muscles. Postural stability was assessed with eyes open and eyes closed. Force steadiness trials were performed with (VIS) and without (NVIS) visual feedback of the force. The coefficient of variation of force (CV) from detrended force segments was taken as a measure of the amplitude of force fluctuations. MVC of the PF muscles was reduced for the O-OA compared with the Y-OA. The O-OA subjects displayed: 1) a greater CV of force for the PF muscles during VIS compared with Y-OA, 2) a significant increase in the CV of force for the PF muscles for VIS compared with NVIS, and 3) reduced postural stability with eyes open and eyes closed compared with Y-OA. Upon pooling the entire sample of older adults, the amplitude of DF force fluctuations during VIS and the degree of postural instability with eyes open were weakly correlated ($r = 0.30$, $P = 0.05$). Advancing age in older populations produces an impaired ability to control PF muscle force and postural instability, especially when

visual feedback is removed and proprioceptive feedback is dominant. The finding that PF force control and postural stability are weakly correlated across the 67-94 year range suggests at least a small contribution of ankle muscle dyscontrol to the postural instability that reduces quality of life for older adults.

Introduction

Age-related declines in maximal muscle force production, submaximal force control[1-5], and postural stability[6-8] negatively impact the ability of older adults to perform activities of daily living[9-13], reduce quality of life, and increase societal economic burden[14]. Various studies have characterized the decline in postural control associated with aging[15] from the perspectives of postural sway amplitude[16], increased center of mass fluctuations[15], force fluctuations under the feet[17], and a decreased ability to correct postural perturbations[6]. Current evidence indicates that decline in postural stability accelerates within the older population[18], concomitant with the acceleration of fall incidence with age in older populations[19]. Negative outcomes from the decline in postural control include increased fall risk[20], and decreased ability to perform activities of daily living[21], as well as increased risks of morbidity[7] and mortality[22]. Adoption of the "ankle strategy"[15] may also occur in which postural control is influenced to a greater degree by ankle torque output. Increased incidence of ankle strategy use is associated with aging[6,17,23,24] and is likely due, in part, to degraded modulation of reflex input by inhibition secondary to decreased sensory acuity[25]. The adoption of the ankle strategy, in combination with the decline in ankle force control associated with aging[26,27], suggests that altered force control at the ankle may contribute to the loss of postural

stability. The plantarflexors, in particular, likely play a significant role in postural stability in aging[27] because during quiet standing they act to counteract the continuous dorsiflexion torque produced by the fact that the center of mass is slightly anterior to the sagittal plane rotation center of the ankle[28].

Normal human aging degrades the ability to produce steady muscle forces, a notion supported by many studies that examined the control of muscle groups isolated in an experimental rig[1-5]. Alterations in central processing of sensory input with age contribute to this dyscontrol of muscle force.[29] For example, central processing of visual input for the control of muscle force output is degraded with age despite the need for a greater reliance on this sensory system[30,31]. This decline has been investigated in experiments that manipulated the amount of online visuomotor correction of force output. The findings suggest that impaired visuomotor processing, and the subsequent fluctuations in descending motor command, is a contributor to decreased force steadiness[32]. This age-associated impairment of visuomotor processing and a decline in overall sensory acuity, leading to a greater reliance upon vision to maintain posture, suggests that visuomotor processing of isolated muscle groups may be associated with postural stability when visual feedback is present.

A variety of proprioceptive inputs (e.g. vestibular [33-36], mechanoreceptors including muscle spindles and cutaneous sensors[34,37,38]) decline in function and/or processing with age, impacting postural control. A study performed by Masani *et al.* suggested that proprioceptive afferent input at the ankle contributes to muscle activation for postural control[39]. During free standing, surface electromyogram (sEMG) activity at the soleus and ankle torque was significantly greater than that found at rest. With

anterior support perpendicular to the shank, soleus sEMG activity and ankle force output were similar to that found at rest. These findings provide a more complete scheme regarding the impact of ankle proprioception on postural sway in that torque applied at the ankle, in addition to body sway velocity[39], activates muscle activity for postural maintenance.

The relationship of force variability in an isolated muscle group with functional ability in real-world tasks has previously been characterized in small muscle groups, including the first dorsal interosseus. For example, force control tasks that included exertion of a constant trajectory[9,40] or movement to a discrete target[41] were correlated with performance on dexterity tasks[40-46]. Although neuromuscular force control about the knee has been found to be associated with improved function in activities of daily living[47], ambulation[9], and postural control[48], few studies have investigated the impact of neuromuscular control of ankle force on functional activities. Those that have suggest that ankle force control impacts postural stability[48,49]. The coefficient of variation of isometric plantarflexor force output at 2.5% of maximal voluntary contraction, for example, has been shown to be correlated with the coefficient of variation of the center of pressure during quiet standing[49]. This potential relationship is bolstered by evidence that sEMG activity at the soleus precedes alteration of center of pressure and that torque output at the ankle is reflected by center of mass displacement during quiet standing[50]. Although a few studies have found correlations between force variability in large muscle groups and postural stability or functional mobility[9,20,51], there is a relative lack of information on these relations in older adults across a significant age range.

Preliminary data collected for this study suggest that the rates of decline increase with age in the areas of function, postural control, and force control. These observations suggest ankle force control and postural control could be related and that this relationship may change with age. Furthermore, it is reasonable to expect that an older adult who can exert better control over the force output of their ankle muscles would exhibit greater functional mobility, and vice versa.

Due to the influence of increased age on function, postural control, and force control, the present investigation aimed to characterize differences between the youngest half and the oldest half of a large sample of older adults; a young-old (Y-OA) group vs. an old-old (O-OA) group. It was hypothesized that functional ability, postural control, and force control would decline with age upon comparison of these groups. It was also hypothesized that plantarflexor and dorsiflexor force fluctuations would be related to postural fluctuations to a greater degree in individuals with lesser postural stability. This notion would suggest that degraded ankle muscle control associated with aging impacts real-world function. It was expected that the strongest correlation between ankle force control and postural stability would be demonstrated by the O-OA group. It was furthermore expected that the correlations between force control and postural stability would be greatest without vision as this would reduce any potential effects of visuomotor processing. A second aim of this investigation was to determine the role of visuomotor processing in both ankle muscle control and postural control in Y-OA and O-OA adults. It was hypothesized that visuomotor processing would have a greater effect on both ankle muscle control and postural stability for O-OA compared with the Y-OA group. The results have been presented in abstract form previously[52,53].

Methods

Subjects. In order to examine changes across an older age range, a larger sample of older adults (N = 47, mean age 78.9 ± 1.1 years) was divided into two groups based on the median age: Young-Older Adults (Y-OA, n = 22, 72.6 ± 0.8 years), and Old-Older Adults (O-OA, n = 25, 84.5 ± 1.0 years). Three subjects at the median age were placed into the O-OA group, thus the O-OA group is slightly larger. Participant characteristics are reported in Table 1. The between-group differences in height and mass may be due to a larger proportion of males to females (12/10) in Y-OA and a smaller proportion of males to females (11/14) in O-OA. Males in both groups were found to have greater height ($P < 0.001$, in both groups) and body mass ($P < 0.05$). Subjects neither reported nor exhibited signs or symptoms of neurological disease during a medical examination by a physician, were free from medications known to influence the dependent measures, and reported less than 3 hours per week of low-to-moderate intensity exercise with no intense, purposeful physical training in the previous year. Each subject visited the laboratory on four separate occasions for orientation, plantarflexor force tasks, dorsiflexor force tasks, and postural sway tasks. After orientation to the research procedures, all subjects provided informed consent. The Institutional Review Board of Colorado State University approved all procedures used in this experiment.

Research Setup

Force Production and Steadiness Assessment. The protocol required subjects to perform isometric contractions of the ankle plantarflexor and dorsiflexor muscle groups. Subjects were assessed on their non-dominant side. Subjects were seated in an

adjustable chair, with the foot placed in an adjustable footbed apparatus and secured with a micro-adjustable strap over the dorsal surface of the foot. The upper torso was restrained with a four point harness and the thigh secured with a custom, padded restraining device at the distal thigh. The hip was fixed at ~80 degrees of flexion, the knees at 90 degrees of flexion, and the ankle at 95 degrees. The perpendicular axis of the load cell was aligned with the first phalangeal-metatarsal joint. The sensitivity of the load cell used for each task differed and ranged from 4.1 – 583.5 Newtons per volt. Force signals were amplified and filtered using Coulbourn LabLinc V-series transducer couplers (Coulbourn Instruments, Allentown, Pennsylvania). Analog-to-digital conversion of signals was performed using a Power1401 (Cambridge Electronic Design, Cambridge, United Kingdom). Force data was digitized at 1 kHz, visualized online, and stored for offline analysis using Spike2 version 7.09 (Cambridge Electronic Design, Cambridge, United Kingdom).

Two tasks comprised the force protocol: maximal voluntary contraction and isometric steadiness. For maximal voluntary contraction, subjects performed a three second ramp of isometric force in either plantarflexion or dorsiflexion and maintained a maximal force for approximately three seconds. At least one minute of rest was given between trials to minimize the effects of fatigue. Trials were performed until two maximal force values within five percent of each other were achieved. This was accomplished in three to five trials.

Isometric force matching trials at 2.5% of MVC in ankle dorsiflexion and plantarflexion were performed on separate days. Assessment days were randomized between dorsiflexion and plantarflexion. Subjects were instructed to match a target line

on a 48cm computer monitor placed 60 cm from the subject's eyes. Force matching was performed with vision (VIS) and without vision (NVIS). For VIS, the target force was a bold stationary horizontal line fully across the screen and the subject's force was a horizontal line that moved vertically according to the exerted force (VIS). For NVIS, subjects were verbally coached to the target force and instructed to hold the force at that level with the visual feedback turned off. For each condition the subjects were instructed to maintain the force as steadily as possible. At least one minute of rest was given between each force matching trial. The order of presentation of VIS/NVIS was randomized.

Postural Steadiness Assessment. Subjects stood on two parallel force platforms (model 4060-10, Bertec Corporation, Columbus, Ohio, USA). The heels and balls of the feet were 10% of height apart. Force platform data was digitized at 100Hz, low-pass filtered at 10Hz, and stored for offline analysis using data collection software (Vicon Motus 8.5, Englewood, Colorado, USA). Subjects performed four 60s trials standing quietly with eyes open (QSEO) and with eyes closed (QSEC). The order of QSEO/QSEC trials was randomized within assessment sessions. Subjects were instructed to keep their hands at their sides, look straight ahead at a marked point on the wall, stand as still as possible, and either close or open their eyes depending upon the QSEO/QSEC trial type. Verbal feedback on the passage of time was provided at 15, 30 and 45 seconds. A custom guard rail surrounded the subject in the event of a loss of balance and spotters were present for every trial. Subjects were allowed to sit for rest as long as necessary between trials to reduce any potential influence of fatigue.

Functional Mobility Assessment. The timed-up-and-go and the 5m walk were used to assess functional mobility. For the timed up and go test subjects rose from a seated position without the assistance of their arms, walked forward three meters, turned around, walked back to the seat and sat down. The functional task visit included assessment of lean body mass by dual-energy x-ray absorptiometry. Furthermore, cutaneous sensory threshold at the foot was assessed by averaging the values (g/mm^2) of the lowest Semmes-Weinstein filament sensed at four sites (pulp of the great toe, lateral plantar surface of the foot, medial plantar surface of the foot, and the first dorsal web space) with eyes closed.

Data Analysis. Fluctuations in dorsiflexion and plantarflexion force were characterized by the calculation of the relative amount of force fluctuation [Coefficient of variation of force; CV = [(SD of force/mean force) * 100] during all force matching trials. The SD of force was measured from 10s segments that had been detrended using the DC remove function in Spike2 with a 1s time constant. This procedure removes slow drift (< 0.5 Hz) from the force signal that often occurs in the no-vision task, but retains the force fluctuations[54].

For postural stability data, Vicon Motus software first calculated the center of pressure (COP) from each force platform. netCOP (the weighted average position of COP from each force platform) was determined in the anteroposterior direction via the equation below:

$$netCOP = COP_l \cdot \frac{F_{z(l)}}{F_{z(l)} + F_{z(r)}} + COP_r \cdot \frac{F_{z(r)}}{F_{z(l)} + F_{z(r)}} \qquad (1)$$

Where COP_l and COP_r are the center of pressure under the left and right foot, respectively; $F_{z(r)}$ and $F_{z(l)}$ are the vertical ground reaction force under the left and right foot, respectively. From this calculation, anteroposterior sway (APsway) was computed as the distance from the maximal anterior excursion to the maximal posterior excursion during the duration of the trial. Anteroposterior path length (APpl) was also computed as the aggregate distance of anteroposterior movement during the duration of the trial. All postural measures were normalized to foot length in each subject.

One-way analysis of variance (ANOVA) was used to compare demographic differences between groups. Within (VIS, NVIS) and between-subjects (Y-OA, O-OA) effects were assessed with repeated-measures ANOVA. Correlations were computed using Pearson's R to assess relations between ankle force steadiness and postural stability. α was set to 0.05. Values are presented as (mean ± standard deviation of the mean) in text and (mean ± standard error of the mean) in tables and figures. IBM SPSS version 21 (Chicago, IL) was used.

Results

Subjects. Demographic characteristics of Y-OA (n = 22, 13 men, 9 women) and O-OA (n = 25, 12 men, 13 women) subjects are presented in Table 1. By design, the Y-OA group was significantly younger than O-OA ($P < 0.01$). The Y-OA group was also significantly taller than O-OA ($P < 0.05$). Body mass was greater for Y-OA than O-OA. Body mass index was similar between Y-OA and O-OA ($P < 0.05$). Though lean body mass was greater in Y-OA (than O-OA ($P < 0.05$)), there was no difference in lean body mass as a percentage of body mass between Y-OA and O-OA. Some of the significant

group differences in body mass, height, and lean body mass are presumably due to the greater proportion of men in the Y-OA group, who naturally displayed greater values on those variables.

Functional/sensory tests. Foot sensory thresholds (P = 0.74) were similar between Y-OA (4.42 ± 0.62 g/mm^2) and O-OA (4.48 ± 0.57 g/mm^2). Time taken for the timed-up-and-go task was less for Y-OA than O-OA (10.1 ± 3.69 vs.13.8 ± 5.17 s, P < 0.01). The five meter walk was performed faster by Y-OA than O-OA (3.74 ± 1.47 vs. 4.93 ± 1.66 s, P < 0.01).

Strength values. PF MVC (Figure 1.1) was reduced (P = 0.03) by 26% in O-OA compared with Y-OA. Similarly, DF MVC was also 20% less (P = 0.02) for O-OA compared with Y-OA. When PF MVC was normalized to lean body mass, Y-OA (10.7 ± 0.88 N/kg) were similar (P = 0.38) to O-OA (9.22 ± 0.81 N/kg). Likewise, DF MVC normalized to lean mass was similar (P = 0.24) for Y-OA (5.80 ± 0.24 N/kg) and O-OA (5.44 ± 0.33 N/kg). Due to greater MVC values for the men compared with women in each group, part of the group differences in MVC may be explained by the greater proportion of men in the Y-OA group.

Force fluctuations. Visual feedback effects (Figure 1.2): For the Y-OA group, the CV of force for the DF muscles was similar between VIS and NVIS (P = 0.47). In contrast, for the PF muscles the CV of force was greater for VIS than NVIS (P = 0.05). For the O-OA group the pattern was similar; for the DF muscles the CV of force was not significantly

different between VIS and NVIS (P = 0.17), but for the PF muscles the CV of force was greater for VIS than NVIS (P < 0.01). A vision condition by group interaction was present for the PF muscles (P = 0.02); the difference between visual feedback conditions was significantly greater for O-OA than Y-OA. No such interaction existed for the DF muscles (P = 0.67).

Group differences: The CV of force was similar between groups for DF with vision (P = 0.50), DF without vision (P = 0.37), and PF without vision (P = 0.60). However, for PF with vision the CV of force was significantly greater for O-OA than Y-OA (P = 0.05).

Postural stability. Young-old adults exhibited greater postural stability compared to O-OA in all measures including APsway with vision (P = 0.05), APsway without vision (P = 0.01), APpl with vision (P < 0.01), and APpl without vision (P = 0.01). APpl was also reduced in Y-OA and O-OA with eyes open compared with eyes closed (P < 0.01) in both groups. A vision condition by group interaction was present for both APsway (P = 0.03) and APpl (P = 0.05) such that the difference in APsway and APpl between visual conditions was greater for O-OA (Figure 1.3).

Force steadiness/postural steadiness relations. All older adults (N = 47): For the DF muscles, the CV of force with vision was weakly positively correlated (Figure 1.4) with APpl with vision (r = 0.30, P = 0.05). The CV of DF force with no vision was correlated with APpl with vision (r = 0.39, P = 0.01) and without vision (r = 0.364, P = 0.02). For the

PF muscles, there were generally no correlations but for a slight trend of a correlation between the CV of force with no vision and APpl without vision (r = 0.27, P = 0.08). Within each age group, there were only statistical trends toward moderate correlations. For O-OA, there was a trend approaching significance for CV of DF force without vision vs. APpl without vision (r = 0.429, P = 0.07). For the Y-OA there were a few trends toward correlations; the CV of DF force with vision and APpl with vision (r = 0.40, P= 0.07), and the CV of DF force without vision with APpl with vision (r = 0.40, P = 0.06) and APpl without vision (r = 0.37, P = 0.09).

Force steadiness/functional performance relations. For the whole sample of older adults, only PF CV of force with vision was weakly correlated with the timed-up-and-go (r=0.33, P=0.04) (Figure 4) but not with five meter walk time. For Y-OA, only DF CV of force was negatively correlated with timed-up-and-go (r = -0.45, P = 0.04), and five meter walk time (r = -0.45, P = 0.03). For O-OA, there were no significant correlations of DF or PF steadiness values with timed-up-and-go or 5m walk times.

Discussion

The main goals of this study were to 1) characterize force control, postural, and functional mobility differences between a group of Y-OA (67-77yrs) and a group of O-OA (78-94yrs), and 2) to determine if motor output fluctuations (steadiness) in the ankle muscles was correlated with postural stability and functional mobility. PF force steadiness was impaired at very low forces for the oldest old when visuomotor processing contributed to the control, but not significantly so for the DF. Postural stability and functional mobility was impaired for the O-OA compared with the Y-OA.

However, the amplitude of only the ankle DF motor fluctuations was at best weakly correlated with postural stability across the entire age range of our sample, with essentially no correlations within either the Y-OA or O-OA. The steadiness of the PF muscles was weakly correlated with mobility across the entire age range.

The present study directly addresses a gap in the literature by investigating ankle force control, postural steadiness, and the relation of the two in the context of advanced aging. Similar to previous findings comparing force control in older and young adults[31,32,55], plantarflexor control was diminished in O-OA compared to Y-OA with vision. This difference was ablated upon removal of visuomotor processing (visual force targeting). Diminished submaximal force control associated with aging is well established in a variety of muscle groups[56,57], including the plantarflexor (PF) muscles[26]. The relation of the decline in force control to declines in functional ability has previously been characterized in small muscles such as the first dorsal interosseus, where force control in the isolated muscle was correlated with performance on dexterity tasks[40-46] like producing a controlled trajectory[9,40] or reaching discrete targets[41]. Neuromuscular force control about the knee has been found to be associated with function in activities of daily living[47], ambulation[9], and postural control[48]. Only a few studies have investigated the impact of neuromuscular control of ankle force on functional performance, and they suggest that ankle force control is related to postural stability[48,49].

Similar to the ankle force steadiness findings, the present investigation found postural control to be degraded in O-OA compared to Y-OA. Unlike the force steadiness findings, however, postural control was degraded by removal of vision (discussed

below). This degradation was exacerbated in O-OA compared to Y-OA. The overall increased postural instability reported here agrees with previous studies comparing older and young adults[49] [8,16,58-60], which have characterized the decline in postural control associated with aging[15] from the perspectives of postural sway amplitude[16], increased center of mass fluctuations[15], force fluctuations under the feet[17], and a decreased ability to correct postural perturbations[6]. Teasdale, *et al.*, for example, found postural sway to be increased with age and with regard to response in visual condition alterations in which vision was removed[60]. Similarly, Lin and Woollacott found functional balance to be impaired with age[61]. The present investigation adds to this body of evidence by describing the decline in postural control across a large age range of an older population.

The general notion that motor output variability at the ankle should impact postural stability was suggested by observations that surface electromyogram (sEMG) activity at the soleus precedes alteration of center of pressure and that torque output at the ankle is reflected by center of mass displacement during quiet standing[50]. Furthermore, the coefficient of variation of isometric PF force output at 2.5% of maximal voluntary contraction has been shown to be correlated with the coefficient of variation of the center of pressure during quiet standing[49]. For the studies that have correlated ankle force steadiness with postural stability, the interpretation of these results in the context of older adults or special patient populations is unclear because they have either focused on just young adults[62] or have pooled the values from young and old adults together[49] to compute the correlations. The present investigation partially addressed these voids in that the relation of force control to postural stability in aging was

investigated by comparing Y-OA to O-OA. Ankle force steadiness and postural stability were weakly related when examined across the entire 67-94 year age range of our sample. When divided into Y-OA and O-OA, however, only trends toward significance existed within each group. Thus, it appears that the ability to precisely control fluctuations in motor output during isometric contractions of the ankle muscles does not explain a significant amount of the postural or functional mobility decline in older adults.

We hypothesized that plantarflexor ankle muscle force control would be related to postural stability based on previous investigations[39,63-65]. Older adults commonly employ the ankle strategy during postural control[6,17,23,24], wherein co-contraction of the ankle plantarflexors and dorsiflexors is utilized[66] in order to minimize fluctuations in torque during standing. It is thought that degraded sensory function or a reduced ability to modulate reflex input with pre-synaptic inhibition leads to this phenomenon in which the ankle is stiffened in an attempt to enhance stability[25]. Furthermore, we expected that the plantarflexor fluctuations would be more correlated with postural control than the dorsiflexors, because during standing the center of mass is slightly anterior of the center of the ankle. This necessitates plantarflexor activation to counteract the gravity-induced dorsiflexion torque and maintain upright stance[50]. Plantarflexor activation is also temporally correlated to postural sway[67] which suggests that the plantarflexors are most likely to be the primary muscle group responsible for control of ankle torque in the anterior-posterior direction during quiet standing. The negative effect of isolated plantarflexor fatigue on postural sway also suggests that variability in plantarflexor output plays a role in postural control[64,68,69]. For example, different plantarflexor fatigue protocols, including repeated calf raises[68], isometric force production[69], and dynamic

force production[64] to failure, induced increases in APsway compared with pre-fatigue trials. The observation that fatigue induced in just the plantarflexors can increase postural sway supported our hypothesis that plantarflexor force control would be related to postural stability.

Previous studies have investigated the correlation of ankle force control with postural stability[49-51,62,64,68,70]. Oshita and Yano assessed anterior-posterior postural sway and plantarflexor force fluctuations at 10% and 20% of MVC in young men[62]. In contrast to the present study, measures of ankle muscle force fluctuations were found to be correlated with measures of postural control. A key difference in study design may account for this disagreement. While the present study focused on a mixed sample of older adults, the Oshita and Yano study only reported data from young males. Their finding of a relation of ankle force control to postural stability in young adults, together with our finding of a lack of such a relationship in the old, suggests the presence of a shift in postural maintenance strategy[15] associated with age whereby the utilization of sensory input (e.g. proprioception, vestibular sense, vision) in postural maintenance is altered. Speaking specifically to this explanation in outcome differences, Teasdale, *et al.* investigated the impact of altered visual feedback on postural maintenance in young and older adults[60]. Young adults were better able to rapidly adapt to a no vision condition by normalizing their postural sway to that of the vision condition compared with the response of the older adults. This finding suggests that older adults have a greater reliance on vision and a decreased reliance on proprioception in postural maintenance as compared to young adults. This age-related shift in postural strategies could fundamentally alter the relation of ankle force control to postural stability.

Differences in the outcome measures for force fluctuations may also explain the differences in findings. The standard deviation of force was used by Oshita and Yano to assess force steadiness whereas the present study used coefficient of variation of force. While both measures provide information regarding force fluctuations, CV of force represents the fluctuations normalized to mean force and therefore allows the comparison of the relative magnitude of fluctuation between people with different strength levels. Because the CV of force accounts for differences in force levels and signal-dependent noise driven absolute force fluctuations between individuals, it is likely a more reasonable way to assess group differences and relations to postural fluctuations. Another key methodological difference between the present study and Oshita and Yano was knee position during the assessment of force steadiness. While we placed the knee at a right angle to minimize the contribution of the gastrocnemii, Oshita and Yano performed the testing with the knee straight, a position more like that during standing. The straight knee position may have allowed the subjects to use the gastrocnemii more during the force steadiness task and that may have been similar to the muscle use during the postural tasks. Another methodological difference in force steadiness assessment was the target force. Oshita and Yano utilized 10% MVC while the present investigation utilized 2.5% MVC. This could alter potential relations found between force control and postural stability as greater amount of force output is associated with greater force control[32]. In postural steadiness assessment, the present study utilized force platforms to measure center of pressure while Oshita and Yano utilized a laser-based measure of displacement of the center of the body. As these measures are correlated, it is unlikely that this difference significantly impacts

comparison of these studies. Finally, both postural stability and force steadiness measures were performed only with eyes open by Oshita and Yano whereas the present study performed these assessments both with eyes open and eyes closed to discern the role of visual processing.

Oshita and Yano expanded on their previous study by investigating the effect of isolated plantarflexor steadiness training (isometric force matching at 10% and 20% MVC for four weeks) on postural sway in young men[70]. This training was found to reduce plantarflexor force fluctuations by 21% and postural sway by ~14%, implying that: 1) postural steadiness is related to plantarflexor steadiness, and 2) postural steadiness is plastic and can be improved by isolated plantarflexor motor control training. Again, this study involved only young men whereas the present study focused on older adults. This difference reinforces the notion that a shift in postural control strategy occurs in aging. For older adults, this shift would predict a blunted improvement in postural stability after plantarflexor steadiness training, unlike the significant effect observed for young men.

An investigation more similar to the present study examined the relationship of plantarflexor steadiness at 2.5% MVC with the coefficient of variation of the center of pressure in young and older adults[49]. There was a correlation ($r = 0.62$, $P < 0.01$) between these two variables when the regression was computed on the young and older groups pooled together. Independent correlations for each group were not reported. Visual inspection of the scatterplot depicting this relationship suggests that this correlation may have little to do with a relationship between force steadiness and postural sway, and more to with the independent effect of age on each of these

variables – the data appears to group by age in a relatively discrete manner. Thus, the significant correlation may be an artifact of the differences between young and older adults and not an indicator of the relation between plantarflexor steadiness and postural steadiness. Furthermore, all force steadiness trials performed by Kouzaki and Shinohara were performed with vision. This lack of no-vision trials clouds the interpretation of the results because visual processing has the potential to confound the dependent variables. Differences in force steadiness and postural steadiness found between young and older populations could be due to diminished central visual processing[55].

This study was potentially limited by the position of the knee during assessment of force control. During unperturbed standing the soleus is a primary, active contributor to ankle torque and the gastrocnemii are less active[71-74]. Thus, for isolated muscle steadiness testing the knee was placed at a right angle to maximize the relative contribution of the soleus muscle and minimize the contribution of the gastrocnemii. This necessitated a seated position in our testing apparatus. The differences in the nature of the force control task and postural control task could potentially alter the relative importance of the processes used by the nervous system for control. The vestibular system, for example, provides information on head movement and position to the central nervous system, resulting in changes in the force applied by the plantarflexors and dorsiflexors during standing[35,75]. It is unlikely this contributed significantly to the motor output during the seated ankle steadiness task. Furthermore, the importance of afferent input mechanisms (e.g. cutaneous and muscle mechanoreceptors) from the lower limb to the central nervous system is likely to be less

in a seated position as compared to standing. These signals are used in standing to maintain posture at both a voluntary and reflex level[35,75]. For example, the spindle-mediated stretch reflex is quite sensitive to the small changes in dorsiflexor and plantarflexor length during standing, but not nearly as much during the seated force production task. It is possible that spinal reflexes[76] may exert a significant effect on postural stability during quiet in addition to voluntary force control. Lumbar spinal signaling can also affect postural stability wherein extremely small[77] alterations in dorsiflexor muscle length can initiate a reflex response in which the plantarflexors are activated[36]. Another difference between the force assessment and postural control assessment was the role of visual processing, when allowed. During the visual feedback condition, the force control protocol required online, continuous comparison of the force output with a force target. This creates a focused, attention-demanding visual targeting task for subjects[31,32]. Standing with eyes open, on the other hand, utilizes a more global visual processing scheme whereby static (e.g. the horizon) and dynamic (e.g. slight alterations in visual cues subsequent to postural sway) cues are integrated to both assess and maintain the body's position in space[78]. These fundamentally different visual processing strategies may have weakened the ability to detect a relation between force steadiness and postural steadiness. Another potential limitation of the protocol used in this study is that while the force targeting task was isometric, ankle force output for the control of posture in quiet standing is dynamic in the sense that greater changes in muscle length occur compared with the isometric task. It is reasonable to expect, for example, that the afferent input of primary importance during isometric force matching (particularly with no vision) would be the Golgi tendon organ

and cutaneous pressure receptors for the purposes of force transduction[79]. Golgi tendon organs would also be active during quiet standing, but the slight, continuous change in muscle length during standing would produce more robust, and phasic, feedback from muscle spindles[80]. A second difference between the isometric force task and quiet standing task is that during quiet standing the force output varies, albeit slightly, with sway[81], but the force is static during the force control protocol. Thus, both the nature of the descending motor command and the quality of the proprioceptive and cutaneous sensory feedback would be different between tasks. It is possible that these task-related differences may have obscured any relation between motor steadiness and postural steadiness. Finally, though all subjects reported no diagnosed vestibular disorders or neuropathy, it is plausible that pre-clinical sensory degradation[15,34,35] may have influenced the outcomes by making the afferent signaling characteristics influencing postural stability of these groups more similar than expected.

Conclusions

The ability to maintain postural stability during quiet standing and the ability to minimize force fluctuations in the plantarflexor muscles was impaired for old-old adults compared with young-old adults. Thus, even within the older age range there is a change in neuromuscular physiology that underlies the degradation in these functions. A goal was to determine if a reduced ability to control motor fluctuations in isolated ankle muscles contributed to either postural instability or functional mobility for an individual older adult. Despite a weak correlation between dorsiflexor force steadiness and postural steadiness across the 67-94 year-old age range, there was generally no

evidence of a relationship of either plantarflexor or dorsiflexor muscle force steadiness with postural control within the young-old or old-old adults. Also, despite a weak correlation between plantaflexor steadiness and functional mobility across the 67-94 year age range, there was little evidence of such correlations within the young-old or old-old groups. Thus it appears that the ability to precisely control fluctuations in motor output during isolated, isometric contractions of the ankle muscles does not account for a clinically or functionally significant amount of the postural or functional mobility decline in older adults.

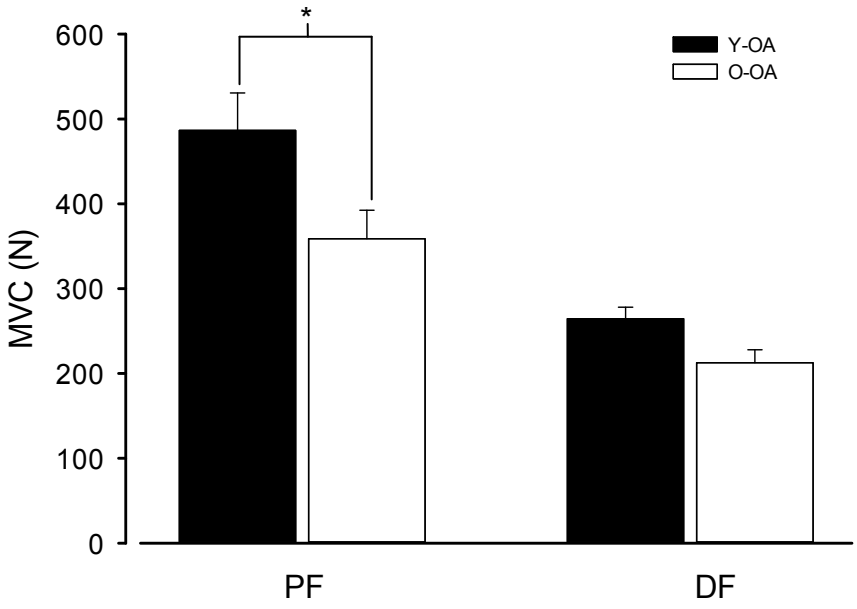
Tables

Table 1.1. Subject Demographics

	Age (y)*	Height (m)*	Mass (kg)*	BMI (kg/m^2)	% Lean Body Mass
Y-OA	72.6±0.76	1.69±0.02	75.6±2.87	26.7±0.76	60.8±1.64
O-OA	84.5±0.96	1.61±0.02	67.6±2.62	26.1±0.77	59.1±1.50

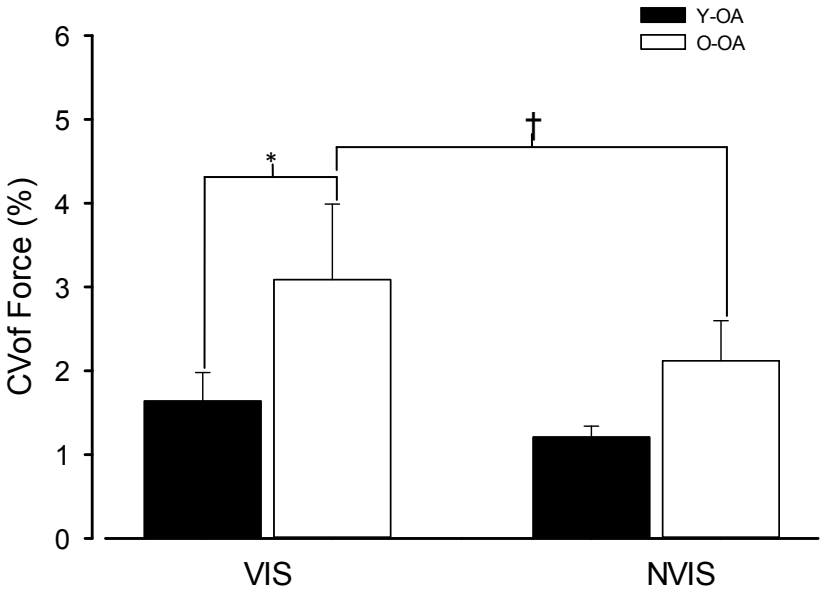
*Between group difference (P<0.05)

Figures



*Between group difference (P<0.05)

Figure 1.1. Plantarflexor MVC. PF MVC was greater (P = 0.03) for Y-OA compared with O-OA as was DF MVC (P = 0.02).



*Between group difference (P<0.05)

† Between condition difference (P<0.05)

Figure 1.2A. Plantarflexor force fluctuations. PF force fluctuations were greater (P < 0.01) in O-OA with vision when compared to without vision. No between-group difference was found in PF steadiness without vision (P = 0.60). A between-group difference was present in PF steadiness with vision (P = 0.05). A vision condition by group interaction was present in PF (P = 0.02) with a greater effect of vision in O-OA.

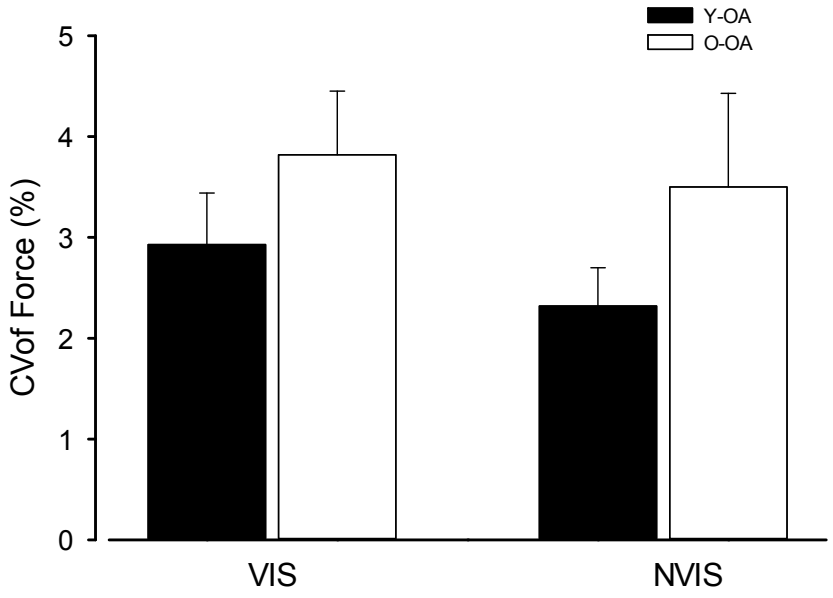
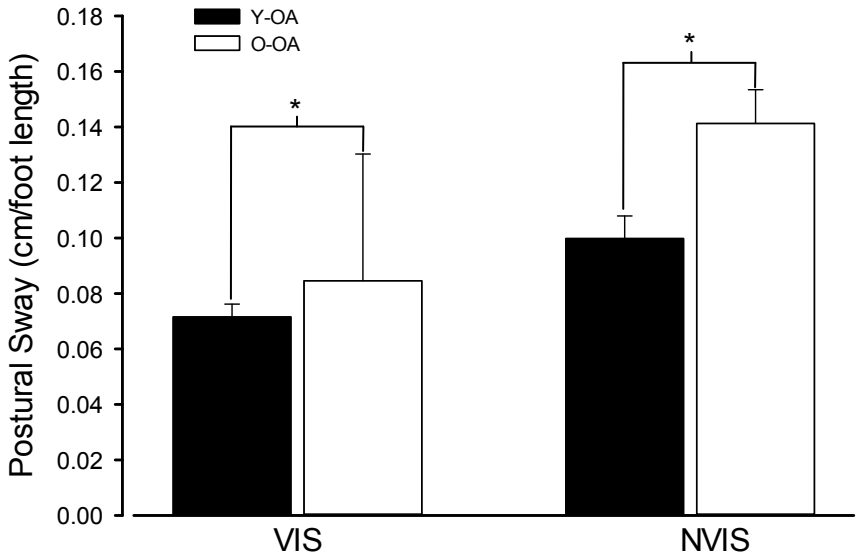


Figure 1.2B. Dorsiflexor force fluctuations. The CV of force for the DF muscles was similar between VIS and NVIS for Y-OA (P = 0.47) or O-OA (P = 0.17). No vision condition by group interaction existed for the DF muscles (P = 0.67). The CV of force was similar between the Y-OA and O-OA groups for DF with vision (P = 0.50) and DF without vision (P = 0.37).



*Between group difference (P<0.05)

Figure 1.3A. Postural Sway. APsway with vision was lesser in Y-OA than O-OA (P = 0.05). APsway without vision was also lesser in Y-OA than O-OA (P = 0.01). A vision condition by group interaction was present (P = 0.03) such that the effect of visual feedback was greater for O-OA.

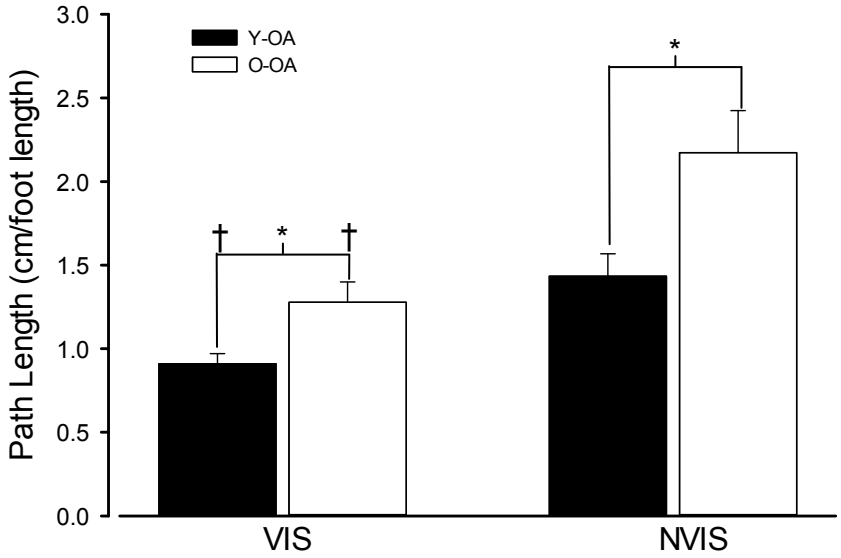


Figure 1.3B. Path Length. APpl with vision ($P < 0.01$), and APpl without vision ($P = 0.01$) were lesser in Y-OA. APpl was also reduced in both Y-OA and O-OA with eyes open compared with eyes closed ($P < 0.01$). A vision condition by group interaction was present for APpl ($P = 0.05$) such that the effect of visual feedback was greater for O-OA.

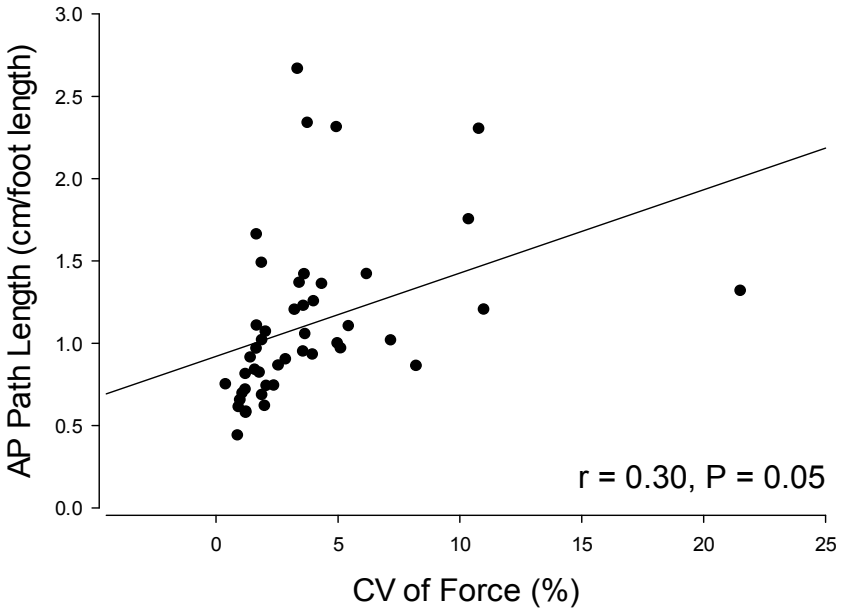


Figure 1.4A. Postural sway/force fluctuation correlations. For the entire sample of subjects the CV of DF force with vision was weakly correlated with APpl with vision (r = 0.30, P = 0.05).

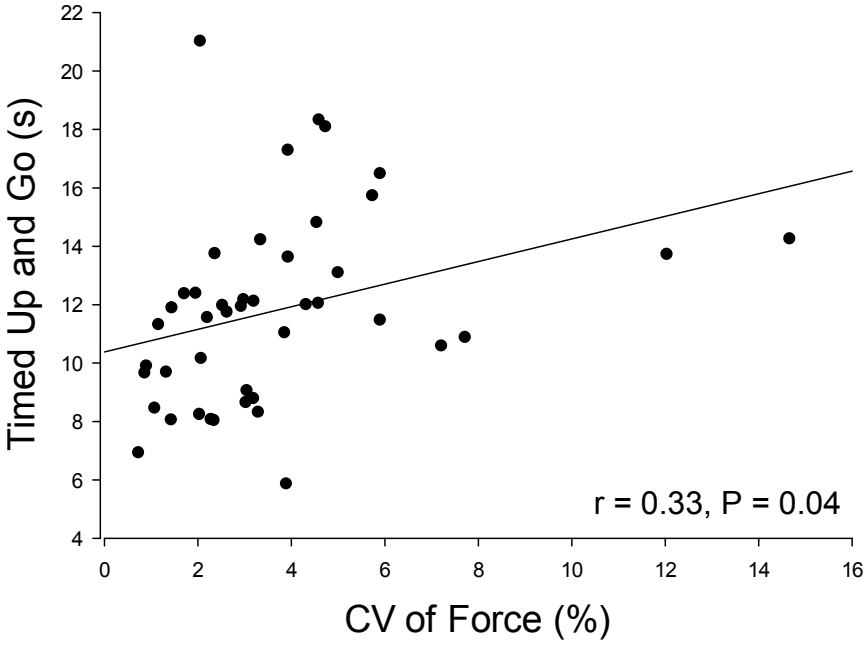


Figure 1.4B. Timed Up And Go/force fluctuation correlations. For the whole sample of older adults, PF CV of force with vision was weakly correlated with the timed-up-and-go (r=0.33, P=0.04)

CHAPTER II – MANUSCRIPT II

Postural steadiness and ankle force control in peripheral neuropathy

Summary

The purpose was to determine 1) the effect of peripheral neuropathy on the variability of motor output in the ankle dorsiflexors and plantarflexors, and 2) the relation between ankle motor variability and postural stability in patients with lower limb peripheral neuropathy (PN). Thirty-two older adults with PN (O-PN), 32 older adults without PN (O), and 12 young healthy adults (Y) underwent assessment of postural stability during quiet standing, isometric strength (maximal voluntary contraction, MVC) and force steadiness (2.5% MVC) of the ankle dorsiflexor (DF) and plantarflexor (PF) muscles. Postural stability was assessed with eyes open and eyes closed. Force steadiness trials were performed with (VIS) and without (NVIS) visual feedback of the force. The coefficient of variation of force (CV) from detrended force segments was taken as a measure of the amplitude of force fluctuations. Force during MVC of the DF and PF was reduced for the O-PN and O subjects compared with the Y. The O-PN subjects displayed: 1) impaired force control in the PF muscles during VIS and NVIS compared with O, 2) impaired force control for the PF muscles in NVIS compared with Y, and 3) reduced postural stability with eyes closed compared with both the O and Y. For O-PN, the amplitude of PF force fluctuations during NVIS and the degree of postural instability with eyes closed were correlated ($r = 0.54$, $P = 0.01$). Peripheral neuropathy in the lower limb produces an impaired ability to control PF muscle force and postural instability, especially when visual feedback is removed and proprioceptive feedback is dominant.

The finding that PF force control and postural stability are correlated for those with PN suggests a contribution of ankle muscle dyscontrol to the postural instability that reduces quality of life for older adults with PN.

Introduction

Peripheral neuropathy (PN) degrades sensory function[82] and reduces the ability of the peripheral nervous system to provide critical afferent feedback to the central nervous system in order to optimize motor output and postural control. Motor neuropathy may follow[83], negatively impacting efferent control of skeletal muscles[84]. This decline in neural function results in proprioceptive[85] and postural[86] deficits that can reduce functional ability[87] and quality of life[88], and increase fall risk[89], morbidity[90], and mortality.[90] Given the projected increase in the elderly population and the diabetic[91] and chemotherapeutic[92] etiology of many PN cases[86,93], the health burden of PN is poised to dramatically increase in prevalence in the coming decades, beyond its current ~2.4% of the global population[94].

As with the postural instability that can accompany normal aging[95], a serious functional problem associated with PN is balance impairment[89,96-98] secondary to sensory degradation[98]. Peripheral neuropathy, however, exacerbates postural instability to an even greater degree than does normal aging[84]. Cutaneous plantar sensation and muscle spindle output are each important to postural stability[49,62,99-101] and are negatively impacted by PN[102]. The decline in cutaneous sensation associated with PN, an initial symptom which continues to progress after onset[103] contributes substantially to postural instability because impaired plantar sensation degrades the

information provided to supraspinal centers about shifting plantar pressures and postural sway[104,105].

Diminished submaximal force control associated with aging is well established in a variety of muscle groups[56,57], including the plantarflexor (PF) muscles[26]. The relation of the decline in force control to declines in functional ability has previously been characterized in small muscles such as the first dorsal interosseus, where force control in the isolated muscle was correlated with performance on dexterity tasks[40-46] such as producing a controlled trajectory[9,40] or reaching discrete targets[41]. Neuromuscular force control about the knee has been found to be associated with function in activities of daily living[47], ambulation[9], and postural control[48]. Only a few studies have investigated the impact of neuromuscular control of ankle force on functional performance, and they suggest that ankle force control is related to postural stability[48,49]. The general notion that motor output variability at the ankle should impact postural stability is strengthened by the observations that surface electromyogram (sEMG) activity at the soleus precedes alteration of center of pressure and that torque output at the ankle is reflected by center of mass displacement during quiet standing[50]. For example, the coefficient of variation of isometric PF force output at 2.5% of maximal voluntary contraction has been shown to be correlated with the coefficient of variation of the center of pressure during quiet standing[49]. For the studies that have correlated ankle force steadiness with postural stability, the interpretation of their results in the context of older adults or special patient populations is unclear because they have either focused on just young adults[62] or have pooled the values from young and old adults together[49] to compute the correlations. The potential role of ankle muscle control in postural stability in PN

patients has not been addressed. There is no research that has characterized the changes in motor output variability in ankle muscles for PN patients, and, accordingly, there is no information on the correlation of impaired ankle muscle control with the excessive postural instability observed in PN patients. This type of information in a PN patient population could eventually inform treatments or interventions to improve ankle control, improve postural stability, improve functional ability, and reduce the risk of falls.

The present investigation aimed to characterize postural control and ankle force control in older peripheral neuropathy patients (O-PN), older healthy adults (O), and young healthy adults (Y). It was hypothesized that postural control with eyes open (EO) and closed (EC), and ankle muscle force control with (VIS) and without vision (NVIS) would be impaired for older adults, and that even greater decline would be found in O-PN. It was also hypothesized that PF and dorsiflexor (DF) force fluctuations would be related to postural fluctuations to a greater degree in individuals with lesser postural stability (i.e. O and O-PN). This outcome would suggest that degraded ankle muscle control associated with aging and further degradation found with neuropathy impacts a real-world function such as postural stability. It was expected that the strongest correlation between ankle force control and postural stability would be demonstrated by O-PN due to the greater changes in that group. Furthermore, it was expected that the correlations between force control and postural stability would be greatest without visual feedback due to the greater reliance on proprioceptive input and the large changes in postural stability that occur for older adults and PN patients when visual input is not available as a sensory input[106]. A second aim was to determine the role of visuomotor processing in both ankle force control and postural control in O-PN, O, and Y. It was

hypothesized that removal of visuomotor processing would reduce force fluctuations for O-PN and O, but not for Y. As has been observed previously, removal of visual feedback was hypothesized to have the greatest detrimental effect on postural control in O-PN, followed by O, with lesser impact in Y.

Methods

Subjects. Thirty-two O-PN (17 female, 15 male), 32 O (23 female, 9 male) subjects, and 12 Y (6 female, 6 male) were studied (Table 1). Written confirmation of PN diagnosis was obtained for each patient from their primary care provider. The O-PN and O subjects were of similar age ($P = 0.33$). Exclusion criteria included overt neurological and/or neuromuscular conditions (with the exception of peripheral neuropathy in the O-PN group), as well as use of psychoactive or tremor-inducing medications. O-PN and Y were of similar height ($P = 0.99$) and were taller than the O group ($P < 0.05$). Body mass and body mass index was similar between O-PN, O, and Y ($P > 0.05$). After orientation to the protocol, subjects provided written informed consent prior to participation in the study. All study procedures were approved by the Human Research Committee at Colorado State University.

The Michigan Neuropathy Screening Instrument was used to further characterize the O-PN group; the neuropathy questionnaire score averaged 4.21 ± 1.85 and the physical examination score averaged 4.64 ± 2.48. These scores align with previous studies with neuropathy patients (e.g. 2.6 ± 1.6, 5.24 ± 1.4, respectively)[82,107] and meet the physical examination score definition of peripheral neuropathy (≥ 2.0)[108]. For a subset of the O-PN subjects Pressure Specified Sensory Device (PSSD) testing was

also performed. At the plantar pulp of the great toe, heel, and dorsum of the foot, measured sensitivity values averaged 86.0 ± 10.7, 78.9 ± 11.9, and 72.1 ± 10.2 g/mm^2, respectively, pooled across the feet. Normative PSSD values in healthy subjects for identical areas are 3.9 ± 4.3, 8.0 ± 8.0, and 4.6 ± 4.9 g/mm^2, respectively. PSSD values ranging from 30.0 to 53.1 have previously been reported in long-term diabetic neuropathy patients[109]. Two point discrimination was performed in a subset of fourteen O-PN at the point of the great toe, though only five O-PN subjects had the ability to feel the points for the test. The average distance at which these O-PN subjects could discern two points of pressure was 1.03 ± 0.32 cm (average of two feet) compared with values from another study of healthy older subjects of 0.13 ± 0.003 centimeters[110]. Peripheral neuropathy patients in other studies have previously demonstrated a two point discrimination distance of 2.5 cm[111]. While this is greater than the average distance noted in our subjects, it must be reinforced that the majority of our subjects could not feel the points of pressure at all, indicating an extreme decline in cutaneous sensation. Fine touch sensation was also assessed in the most affected foot of a subset of 14 O-PN subjects by applying a 10g Semmes-Weinstein monofilament to 10 sites on the foot. They exhibited a 47.1 ± 34% error rate, as compared to a 0.7 ± 1.4% error rate reported elsewhere for healthy subjects[112]. This error rate aligns with previous findings of a neuropathic patient error rate of 55.8 ± 33.5%[113].

Visits. Each subject participated in two visits on separate days. The first visit included orientation to the protocol and postural assessment in the biomechanics laboratory. On

the second day subjects performed ankle force production and control tasks in the Neuromuscular Function Laboratory.

Postural Assessment. Subjects stood on two force platforms embedded in the floor (4060-10, Bertec Corp., Columbus, OH). Center of pressure (COP) data was digitized at 100 Hz for subsequent offline analysis (Motus 8.5, Vicon, USA). Each postural trial consisted of 60 seconds of data collection. The middle 58 seconds of each trial was analyzed. The data were low-pass filtered at 10 Hz (4^{th}-order recursive Butterworth). Each participant completed trials in random order under these conditions, 1) eyes open (EO), standing as still as possible, staring at a mark on a wall 4m ahead, 2) eyes closed (EC), standing as still as possible. A guard rail surrounded the subject. An investigator stood closely behind each subject for protection in the event of balance loss necessitating a step, which did not occur. Subjects were instructed to keep their hands at their sides, look straight ahead at a marked point on the wall, stand as still as possible with heels separated by 10% of height, and either close or open their eyes depending upon the QSEO/QSEC trial type. From these assessments, two center-of-pressure based measures in the anterior-posterior direction were utilized as indicators of postural steadiness as normalized to foot length; postural sway (max anterior COP - max posterior COP, PS), and COP path length (PL).

Force production and control assessment. Force assessments were performed while the subject was seated in a custom, instrumented experimental chair with the hips, knees, and nondominant ankle restrained to 90 degrees. For the O-PN subjects, the

most symptomatic foot was used. The ankle was secured to a custom foot plate fixed to the chair. Load cells were secured under the foot plate to assess DF or PF force. The load cell position was adjustable for different foot lengths. Tension (dorsiflexion) and compression (plantarflexion) force was measured with the load cell directly beneath the first metatarsophalangeal joint so that the force applied was in line with the measurement axis of the load cell. The foot and ankle were firmly secured to the foot plate to maintain both foot position relative to the load cell and the center of rotation of the ankle (lateral malleolus) during both MVC and isometric force matching tasks. The torso and pelvis were restrained with straps and the upper leg was restrained with a rigid mechanism that prevented upward movement during plantarflexion tasks. The purpose of the restraints was to isolate the muscle group of interest as best as possible.

Maximal voluntary contraction (MVC) force in both DF and PF were assessed by instructing subjects to slowly ramp up their force ankle to maximal over the course of three seconds while exhaling and then to exert maximal force for 2-3 seconds. This was performed at least three times until the maximal force from two trials was within 5% of each other. This was accomplished within four trials for most subjects. Strong verbal encouragement was provided. At least 60s rest was provided between MVC trials. Visual feedback was provided by a monitor placed 75 cm in front of the participant.

Isometric force steadiness tasks (2.5% MVC) with (VIS) or without (NVIS) visual feedback were randomized for DF and PF. The order of muscle group was also randomized. To maximize signal-to-noise ratio, the lowest capacity load cell possible was used depending on the target force for the trial. The force signal was amplified (V-series modules, Coulbourn Instruments, USA) and digitized at 1000 Hz (1401 Plus,

Cambridge Electronic Design, UK). The force signal was observed online and recorded for subsequent offline analysis (Spike 2, Cambridge, England). Isometric force steadiness tasks in the VIS condition involved the display of a target force as a bold static horizontal line. The exerted force was represented by another bold horizontal line that moved up and down with changes in force. Subjects were instructed to match the force output line to the target as closely as possible and hold the force as steadily as possible. Isometric force steadiness tasks in NVIS were identical to VIS trials with the exception that the subjects were verbally coached up to the target and then were instructed to hold the force at that level as steadily as possible. Every subject completed two 10s trials in each condition (VIS, NVIS) in randomized order. An overall force steadiness outcome was also calculated by averaging the CV of force for the VIS and NVIS conditions.

Statistics. One-way analysis of variance (ANOVA) with Tukey post-hoc tests was used to determine between-group differences. Repeated measures ANOVA, with group (Y, O,O-PN) as a between-subjects factor and visual feedback condition (VIS, NVIS) as a within-subjects factor, was used to determine the effect of visual feedback and interactions between groups. Pearson's correlations were computed to assess relations between steadiness and postural control. Exact P-values are provided for statistical significance where appropriate. α was set to 0.05. All results are noted as mean ± standard deviation in text, and mean ± standard error in figures. IBM SPSS (Chicago, IL) version 20 was used.

Results

Muscle strength

The MVC force (Figure 2.1A) for the PF muscles was similar ($P < 0.001$) for O-PN and O, and less than Y ($P = 0.27$). Similarly, the MVC force for the DF (Figure 2.1B) muscles was similar ($P = 0.95$) for O-PN and O and was less than Y ($P < 0.001$).

Force fluctuations

Visual feedback and force steadiness. For the older PN patients the CV of force (Figure 2) for the PF (Figure2. 2A) muscles was greater ($P = 0.03$) for VIS than NVIS and the CV of force for the DF (Figure 2.2B) muscles was also greater ($P = 0.001$) for VIS than NVIS ($P = 0.03$). or the older healthy adults the CV of force for the DF muscles was greater ($P = 0.03$) for VIS than NVIS and the CV of force for the PF muscles was also greater for VIS than NVIS ($P = 0.001$). For young adults the CV of force for the DF muscles was not different ($P = 0.22$) between VIS and NVIS but the CV of force for the PF muscles was greater ($P = 0.05$) for VIS than NVIS.

Differences in force steadiness between groups. For the DF muscles, the CV of force with VIS tended to be greater for O-PN than Y ($P = 0.07$), was similar for O-PN and O groups ($P = 0.70$), and was similar for O and Y groups ($P = 0.23$). For NVIS, there were no differences between O-PN, O, and Y groups ($P > 0.10$). For the PF muscles, the CV of force with VIS tended to be greater for the O-PN vs. O group ($P = 0.08$), was greater for the O-PN vs. Y group ($P = 0.003$), and similar between the O and Y group ($P = 0.17$). For NVIS, the CV of force was greater for the O-PN than the O

group (P = 0.001) and Y group (P < 0.001), and similar between the O and Y groups (P = 0.82).

Group differences in steadiness pooled across visual conditions. The CV of force was also expressed as an average of the VIS and NVIS conditions to produce a representative, pooled, steadiness value for an individual. For the DF muscles, the pooled CV of force was not significantly greater for O-PN (5.06 ± 3.25%) compared either with the O group (4.36 ± 3.31%, P = 0.70) or with the Y group (2.73 ± 0.96%, P = 0.09). The O group and Y group were statistically similar (P = 0.27). For the PF muscles, the pooled CV of force was greater for O-PN (4.22 ± 2.74%) than O (2.45 ± 1.58%, P = 0.001) and Y (1.48 ± 0.65%, P = 0.004). The O and Y groups were similar (P = 0.32).

Postural fluctuations

Visual feedback effects. For the O-PN group, PS (min-max A/P) (Figure 3A) was 64% greater (P < 0.001) for the NVIS condition compared with VIS. Similarly, path length (PL) (Figure 3B) was 74% greater (P < 0.001) for the NVIS condition compared with VIS (3.43 ± 0.445 cm/foot length). For the O group, PS was 22% greater (P < 0.001) for NVIS compared with VIS. Similarly, PL was 29% greater for compared with VIS. For the Y group, PS was similar (P = 0.16) for VIS and NVIS. Path length, however, was greater (P = 0.01) for NVIS than VIS.

Group differences in postural stability. Postural sway: With visual feedback, there were no differences in PS between the O-PN, O, and Y groups (P = 0.7 to 0.9, Figure 3A). Without visual feedback, PS was significantly greater for the O-PN group compared with O (P = 0.01) and compared with Y (P = 0.01), with no differences between O to Y (P = 0.68). Path length: With visual feedback, PL was similar for O-PN and O (P = 0.16) and greater for the O-PN group compared with the Y group (P = 0.01). Without visual feedback, PL was greater for the O-PN group than the O group (P < 0.001) and the Y group (P < 0.001) but not different the O group and the Y group (P = 0.35).

Force steadiness/postural stability correlations

Peripheral neuropathy patients

None of the postural stability measures were correlated with dorsiflexor or plantarflexor strength (P > 0.05).

For the postural sway with visual feedback outcome variable, there were no correlations with steadiness measures for either muscle group: CV of force for DF VIS (P = 0.52), DF NVIS (P = 0.91), PF VIS (P = 0.86), or PF NVIS (P = 0.35). Postural sway without visual feedback, however, was correlated with the plantarflexor measures: - both the CV of force for PF VIS (R = 0.43, P = 0.04) and PF NVIS (R = 0.40, P = 0.05) - but not with CV of force for DF VIS (P = 0.83) and DF NVIS (P = 0.93).

A similar pattern emerged for the path length outcome variable. Path length with visual feedback was not correlated with any steadiness measure: CV of force for DF VIS (P = 0.56), DF NVIS (P = 0.72), PF VIS (P = 0.09), or PF NVIS (P = 0.16). However, path length without visual feedback was correlated with the plantarflexor steadiness outcomes: PF VIS (R = 0.51, P = 0.01) and PF NVIS (R = 0.54, P = 0.01,

Figure 4), but not with the dorsiflexor steadiness outcomes: CV of force in DF VIS (P = 0.30) and DF NVIS (P = 0.89).

Older healthy adults

As with the PN patients, there were no correlations between postural stability outcome measures and MVC force for either muscle group.

The postural sway with vision outcome variable was not correlated with the CV of force in DF VIS (P = 0.99), DF NVIS (P = 0.41), or PF VIS (P = 0.31), but was moderately correlated with PF NVIS (R = 0.41, P = 0.02). Likewise, postural sway without vision was not correlated with CV of force in DF VIS (P = 0.31), DF NVIS (P = 0.23), or PF VIS (P = 0.12), but was moderately correlated with PF NVIS (R = 0.47, P = 0.01).

The path length with vision outcome variable was not correlated with CV of force in DF VIS (P = 0.11) or DF NVIS (P = 0.08), while moderate correlations did exist with PF VIS (R = 0.42, P = 0.02), and PF NVIS (R = 0.58, P < 0.01). Path length without vision was not correlated with CV of force in DF VIS (P = 0.31), DF NVIS (P = 0.23), or PF VIS (P = 0.12), but was moderately correlated with PF NVIS (R = 0.47, P = 0.01).

Young healthy adults

Unlike the two older groups, there was a negative correlation between postural sway with vision with both DF MVC (R = -0.58, P = 0.05) and PF MVC (R = -0.62, P = 0.03), but no correlations between postural sway without vision and DF MVC (P = 0.63) or PF MVC (P = 0.23). The path length outcomes were not correlated with any steadiness outcome (P > 0.05).

There were generally no correlations between postural stability outcomes and force steadiness in the young group. For postural sway with vision there were no correlations with the steadiness measures: CV of force in DF VIS (P = 0.53), DF NVIS (P = 0.08), PF VIS (P = 0.24), or PF NVIS (P = 0.48). Similarly, there were no correlations between postural sway without vision and CV of force in DF VIS (P = 0.75), DF NVIS (P = 0.98), PF VIS (P = 0.21), or PF NVIS (P = 0.67).

Likewise for the path length variable with vision, there were no correlations with CV of force in DF VIS (P = 0.73), DF NVIS (P = 0.38), PF VIS (P = 0.22), or PF NVIS (P = 0.59). For path length with no vision, there were no correlations with CV of force in DF VIS (P = 0.45), DF NVIS (P = 0.65), PF VIS (P = 0.77), or PF NVIS (P = 0.34).

Discussion

This study sought to determine 1) the effect of peripheral neuropathy on the ability to control low forces in the ankle muscles of older adults, and 2) the extent to which changes in the control of the ankle muscles are correlated with the postural instability observed in older adults with peripheral neuropathy. Subjects with peripheral neuropathy did not exhibit greater muscle weakness, but their ability to minimize motor output variability during low force isometric contractions was impaired. For those with peripheral neuropathy, when visual feedback was not contributing to the postural task, plantarflexor motor variability was relatively consistently correlated with postural stability. Individuals with a relative inability to control their ankle muscle force also tended to exhibit the greatest postural instability. This suggests a motor output component to the balance impairment of older adults with peripheral neuropathy.

Maximal force. Compared with the young subjects, PF strength was reduced by 57% for the PN patients and 56% for the old adults. This finding was mirrored in the DF muscles, with greater values for young subjects but little difference between older adults and neuropathy subjects. For the plantarflexors, this finding reflects the well-documented effect of aging on strength[5,32,114] and suggests little effect of PN on maximal muscle force for this sample of PN patients. This observation is in contrast with other findings of significant strength loss in neuropathy patients[115-119]. It is thus perhaps the case that the PN patients in the current study did not exhibit the characteristics of the other studies, or that our sample size was insufficient to detect the differences that would be expected between young and old adults. The mean age of the peripheral neuropathy patients in the present investigation is also greater than that of previous studies demonstrating strength loss associated with PN (e.g. 72 ± 7.9 vs. 63 ± 16.1 years[115]) as is the mean age of the older control subjects (e.g. 75 ± 7.6 vs. 62 ± 16.3 years[115]). The possibility exists for a normalization of strength between peripheral neuropathy patients and similarly aged healthy older adults in advanced old age with the decline in ankle strength in young-old compared to old-old healthy subjects[120]. The lack of difference in ankle strength could also be accounted for by duration of peripheral neuropathy. Bokan (2011) found a relationship between duration of diabetes and muscle strength[121]. The peripheral neuropathy patients in the present investigation may simply have been affected by peripheral neuropathy for a briefer period of time as compared to other studies. The literature on dorsiflexor strength and aging is not unequivocal; some studies have failed to find differences in dorsiflexor strength between young and old adults[42,45-47], but other studies have[122,123]. Alternatively, a preservation of

dorsiflexor muscle strength could exist in both healthy aging and peripheral neuropathy. For example, Hasson and Caldwell suggested that the preservation of dorsiflexor force production is secondary to similar amounts of daily physical activity (e.g. walking) between age groups[124]. The lack of strength difference for the peripheral neuropathy subjects and the general lack of a correlation between muscle strength and postural stability is suggestive that for these groups of subjects strength did not contribute to the fluctuations or maximal amount of postural sway during quiet standing.

Force fluctuations. Motor output variability in the plantarflexors was clearly impaired for the peripheral neuropathy patients compared with similarly-aged older adults. This was especially so for the NVIS condition during which only proprioceptive feedback was available for online sensory feedback. There is very little information available on force variability in the ankle muscles of peripheral neuropathy patients. A previous study showed degraded passive ankle tracking ability in peripheral neuropathy patients, suggesting that the degradation of proprioceptors also is implicated along with the loss of sensory function from cutaneous pressure receptors[125].

Numerous previous studies have described differences in force control between old and young adults when visual feedback contributes to the task, with similar values for force variability when visual feedback and the need for the attendant visuomotor processing is removed[26,31,32] . This visual feedback-dependent age effect on force steadiness has been attributed to impaired visuomotor processing in older adults[55,126]. However, for the peripheral neuropathy patients the force fluctuations without visual feedback remained elevated above that for old and young adults. This novel finding

suggests that peripheral neuropathy degrades force control in addition to the aging effect for both VIS and NVIS. Degraded force control without vision for peripheral neuropathy patients is presumably due to decreased afferent feedback about the mechanical state of the lower limb[82,102,125,127,128]. Van Deursen, *et al.* elegantly demonstrated as much by dynamically rotating one ankle through a series of prescribed angles and asking young healthy subjects, peripheral neuropathy patients, and matched controls to match the angle with the contralateral ankle[125]. Young subjects were 0.02 ± 3.48, matched controls were -3.31 ± 5.09, and peripheral neuropathy patients were -4.26 ± 5.09 degrees in error, demonstrating proprioceptive degradation associated with peripheral neuropathy. Proprioception is diminished in peripheral neuropathy[129], thus it is likely that the reduction of force control during isometric contractions arises from dysfunction of neurons/receptors conveying information regarding force in the muscle or skin. This notion is supported by previous description of proprioceptor dysfunction in peripheral neuropathy[125]. Upon application of a vibratory stimulus to enhance muscle spindle function, old adults demonstrate enhanced ankle joint movement perception, whereas neuropathy patients demonstrate a blunted enhancement[125]. Cutaneous mechanoreceptors have also been demonstrated to have a higher mechanical threshold in peripheral neuropathy compared to old adults[130]. Since the target forces for the isometric task were quite low, the forces on the skin and in the muscle were also low. For the peripheral neuropathy patients, the reduced acuity of cutaneous and muscle sense could affect the ability to detect, and therefore control, force output both with and without vision. Finally, although sensory impairment is the dominant and early presentation in peripheral neuropathy, there also remains the possibility that the

degraded control was in part due to impaired efferent transmission to the muscle via degraded motor pathways[115]. That said, the likelihood of this is reduced by the observation that our peripheral neuropathy subjects exhibited minimal muscle strength loss. To our knowledge, these are the first data that describe impaired low-force isometric steadiness in the plantarflexors in older adults with peripheral neuropathy.

Postural stability. When visual feedback was available, postural stability was similar between peripheral neuropathy patients, older adults, and young adults. This has been observed previously[84,131-135] and speaks to the dominant weight of visual feedback in the mix of afferent flow that inform the CNS during postural tasks. However, without the benefit of visual feedback, postural stability was significantly impaired compared with the other groups - a 1.7-fold increase in variability for PN patients compared with a 1.25-fold increase for older adults - suggesting a substantial decline in proprioceptive input for the peripheral neuropathy patients and a greater reliance on visual feedback when it is available. The postural instability observed in our peripheral neuropathy subjects agrees with previous investigations[131-136]. One relatively early investigation on the effect of peripheral neuropathy on postural control was performed by Simoneaeu et al[137]. Older subjects with diabetic neuropathy O-PN exhibited a 21% greater anterior-posterior sway range than age-matched diabetic patients with no peripheral neuropathy and 27% greater AP sway range than healthy age-matched control subjects. These findings were replicated by Katoulis, *et al.* who showed that postural stability was diminished by 21% in diabetic neuropathy patients compared with to age-matched diabetic patients without peripheral neuropathy and age-

matched non-diabetics[133]. More recently, an investigation performed by Kim and Robinson compared the relationship of postural instability to slip perturbation (by use of a force platform displacement system) in diabetic neuropathy patients and healthy aged-matched controls.[134] Diabetic O-PN demonstrated greater anterior-posterior center of pressure deviation in response to slip perturbation than the healthy subjects, suggesting that peripheral neuropathy not only degrades the response to small postural shifts like those encountered during quiet standing, but also affects the ability to respond to larger amplitude perturbations. In the current study, the decreased ability to sense plantar pressure likely contributed to the greater postural sway in the peripheral neuropathy subjects compared with the older and young adults. This decrease in sensation has previously been noted upon comparison of normal values collected from healthy subjects using the Pressure Specified Sensory Device to those from peripheral neuropathy patients. Pressure applied is typically 90% increased at the great toe, and 88% greater at the heel in peripheral neuropathy patient populations[109]. The likelihood of sensing the application of a ten gram Semmes-Weinstein filament at ten prescribed locations on the foot was also 37% decreased in O-PN compared to normal values for individuals without peripheral neuropathy[138]. Two-point discrimination outcomes at the great toe also demonstrate a diminished level of plantar sensation, with a 94% greater two-point distance necessary to sense the discrete points when compared with young adults[139]. Our findings regarding impaired postural control, in conjunction with reduced plantar sensation, agree with a study in which diabetic neuropathy patients with impaired Semmes-Weinstein filament sensibility displayed greater postural instability

compared with diabetic neuropathy patients with normal Semmes-Weinstein values, and healthy control subjects[140].

Interestingly, findings from the present study and those regarding reduced lower limb sensation align well with a postural stability strategy posited by Cavanagh, *et al.* in which neuropathic subjects may purposefully employ greater amounts of baseline sway and increased responses to perturbation in order to boost the amount of afferent feedback and maintain postural stability in the face of decreased proprioceptive feedback from the periphery[129,131]. Our results may lend support to the existence of this postural strategy, in that postural sway was increased without visual feedback to a greater degree for peripheral neuropathy subjects compared to older adults, potentially suggesting a need for exploring the boundaries of sway to obtain greater peripheral feedback for maintenance of posture.

Force steadiness – postural stability correlations. During standing, the PF muscles[24] are activated at low levels to control ankle torque and limit anterior excursions of the center of pressure and center of body mass around the base of support.[50,141] Thus, in addition to the contribution of age-related weakness[142], impaired control, or greater variability, of plantarflexor torque could contribute to the postural stability issues observed in the elderly[15]. Furthermore, both the fluctuations in ankle torque during standing and the plantarflexor force fluctuations present during steadiness tasks are predominantly of similar low frequencies (0-3 Hz)[50,141], which bolsters the hypothesis that force unsteadiness and postural instability could be related.

A very small body of literature has recently suggested a correlation between postural steadiness and ankle force steadiness. Oshita and Yano (2012), for example, assessed the displacement of the center of mass during standing and submaximal PF force steadiness in young men[62]. In contrast to our young subjects, they found a correlation between anterior-posterior mass displacement and force fluctuations at 10% MVC. This relationship can be mechanistically predicted as alterations in the center of pressure during quiet stance activate a variety of muscles in the lower limb, including the soleus, to maintain upright stability[50]. This relationship is also reflected in assessments of physical function. Single-leg standing balance, for example, is moderately negatively correlated with force fluctuations at 20% MVC[143].

For the older adults with peripheral neuropathy, the data from the current study suggests moderate correlations between postural stability – only with the eyes closed - and force steadiness in the plantarflexor muscles, with no correlations involving the dorsiflexors. This is in slight contrast with the non-neuropathic older adults, who exhibited some moderate correlations, albeit inconsistent, under both postural visual conditions. Between-group inspection of these correlation schemes suggests an increased reliance on vision during postural maintenance for the older peripheral neuropathy subjects, presumably due to decreased afferent input from the lower limb[105,144]. A lack of plantar pressure sensitivity could reasonably contribute to a greater reliance on visual input during quiet standing. This notion of a lack of pressure sensitivity is bolstered by the decreased amplitude of sensory nerve action potentials observed in O-PN[127] which may, in turn, contribute to output variability[65]. Increased delays in system input, processing and output lead to concomitant decreases in force

control about the ankle thereby leading to potentially decreased postural stability[65]. This notion is logical from the perspective of peripheral neuropathy as decreases in afferent signal strength secondary to a reduced abundance of sensory neurons[128] may lead to an impaired likelihood of action potential initiation at target neurons. This decreased likelihood of action potential initiation effectively increases the amount of time between stimulus and action and reduces the amplitude of sensory input - a greater stimulus would be necessary to elicit the central neural response. Proprioceptive input may also play a role in postural maintenance and follow the open loop system model. Fitzpatrick and McCloskey found ankle rotation to provide feedback regarding body sway when they experimentally controlled for vision and vestibular signaling[145,146] by blindfolding the subject while simultaneously balancing an inverted pendulum equivalent to their own body mass with the ankle dorsiflexors and plantarflexors.

A study performed by Masani *et al.* also suggests that proprioceptive afferent input at the ankle contributes to muscle activation for postural control[39]. During free standing, sEMG activity at the soleus and ankle torque was significantly greater than that found at rest, as expected. When anterior shank movement was prevented by a mechanical restraint, soleus sEMG activity and ankle force output were similar to that found at rest. These findings demonstrate that the torque applied at the ankle by postural sway activates muscles to maintain posture by muscle spindle mediated reflex action. A diminished ability to sense this torque in peripheral neuropathy would likely negatively impact postural stability and force control which could, in turn, account for the differences noted between older neuropathic adults, health older adults, and young adults.

Recent investigations suggest that restoration of postural stability may be possible. Four weeks of steadiness training, consisting of five sets of 60-s constant force tasks at 10% and 20% MVC, was focused on just the plantarflexors[70]. The standard deviation of the center of mass during the measure of postural stability, and was reduced during quiet standing trials as a result of the training. It is possible that this mode of training, or other forms of training that require precise control of the ankle muscles[147,148] could improve the postural stability of older adults with peripheral neuropathy[149,150].

Limitations

These data are limited to the extent that we do not have objective information on ankle or foot sensory acuity for the healthy older adults to positively ensure that they did not have neuropathic symptoms. Also, vestibular dysfunction, which could produce postural dyscontrol especially when visual feedback is removed[151], was not objectively determined with a physical test. These limitations are mitigated, however, by 1) the fact that we queried the healthy older adults about any neurological problems and specifically about any problems with their feet, 2) the physician-confirmed diagnosis of neuropathy for the older adults in the peripheral neuropathy group, 3) objective measures that clearly denote the neuropathic sensory status in the peripheral neuropathy group, and 4) specific queries during the physical examination about vestibular function. In future research, this weakness could be alleviated by performance of the Clinical Test of Sensory Integration and Balance[152] or the Sensory Organization Test.[153] Proprioception at the ankle contributes to postural stability[102], thus

objective measures of joint movement perception or joint position perception[154] would strengthen the results.

Conclusion

This study sought to describe the steadiness of ankle muscle force in older adults with peripheral neuropathy compared with healthy older adults, and to assess the degree to which the ability to control force variability at the ankle was correlated with the ability to minimize postural sway during quiet standing. Our finding that force steadiness was impaired for the plantarflexors of older adults with peripheral neuropathy suggests that the sensory and/or motor effects of peripheral neuropathy produce significant alterations in motor control of an isolated muscle group. The impaired motor output of this critical controller of ankle torque appears to be related to the ability to maintain the center of mass in a stable fashion over the base of support, which is an important feature of daily functional ability.

Tables

Table 2.1. *Subject Characteristics*. O-PN were older than the Y (P<0.001) as were the O (P<0.001). The O were of lesser height than both the O-PN (P = 0.01) and the Y (P = 0.03).

	Peripheral neuropathy	Older healthy	Young healthy
Age (yr)[*†]	72.2 ± 7.9	74.9 ± 7.6	23.2 ± 3.4
Height (m)[*‡]	1.7 ± 0.1	1.6 ± 0.1	1.7 ± 0.1
Mass (kg)	82.9 ± 15.3	74.8 ± 15.4	72.3 ± 13.3
BMI (kg/m^2)	26.8 ± 8.5	29.1 ± 5.7	25.1 ± 3.7

*P ≤ 0.05, O vs. Y

†P ≤ 0.05, Peripheral neuropathy vs. Y

‡P ≤ 0.05,.Peripheral neuropathy vs. O

Figures

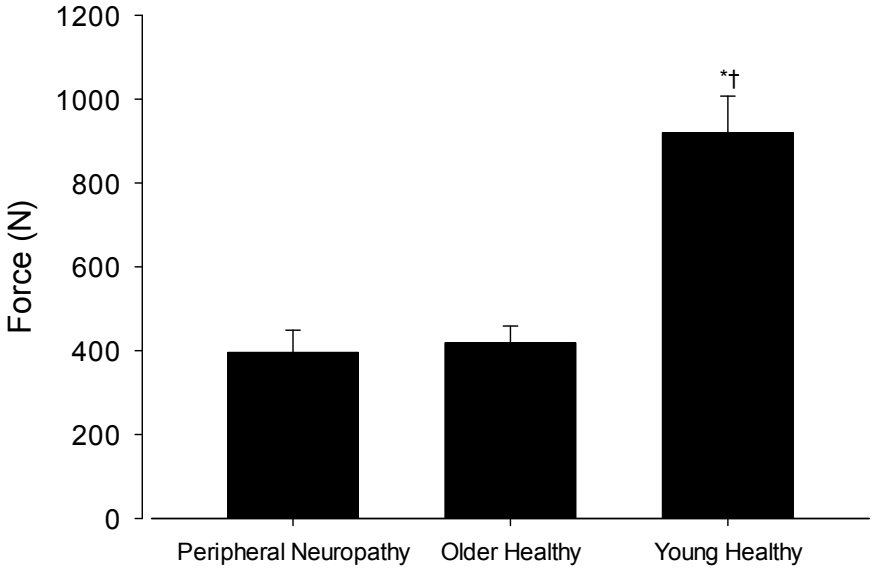


Figure 2.1A. Plantarflexion MVC

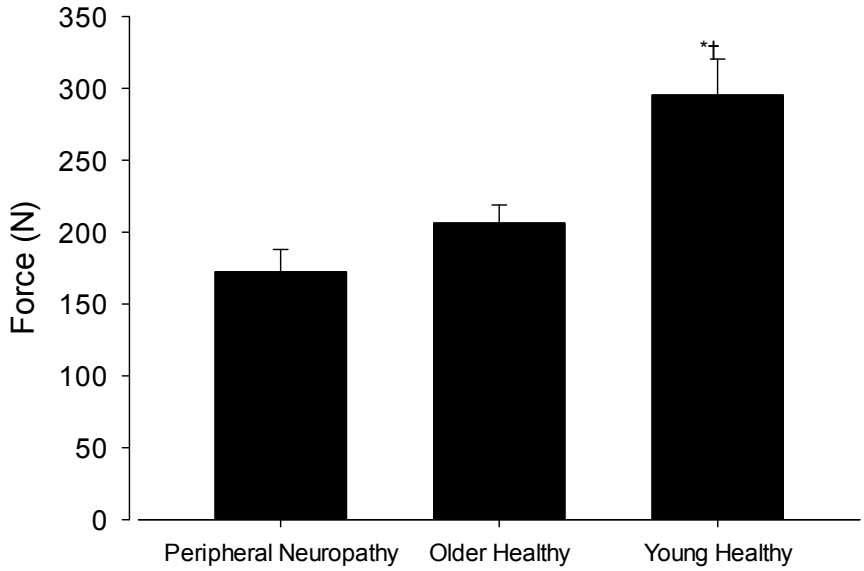


Figure 2.1B. Dorsiflexion MVC

*P ≤ 0.05, O vs. Y

†P ≤ 0.05, O-PN vs. Y

Figure 2.1. Maximal Voluntary Contraction. O-PN and O were found to have a lesser MVC than young subjects (P < 0.01, both comparisons) in DF. O-PN and O were also found to have a lesser MVC than young subjects (P < 0.01, both comparisons) in PF.

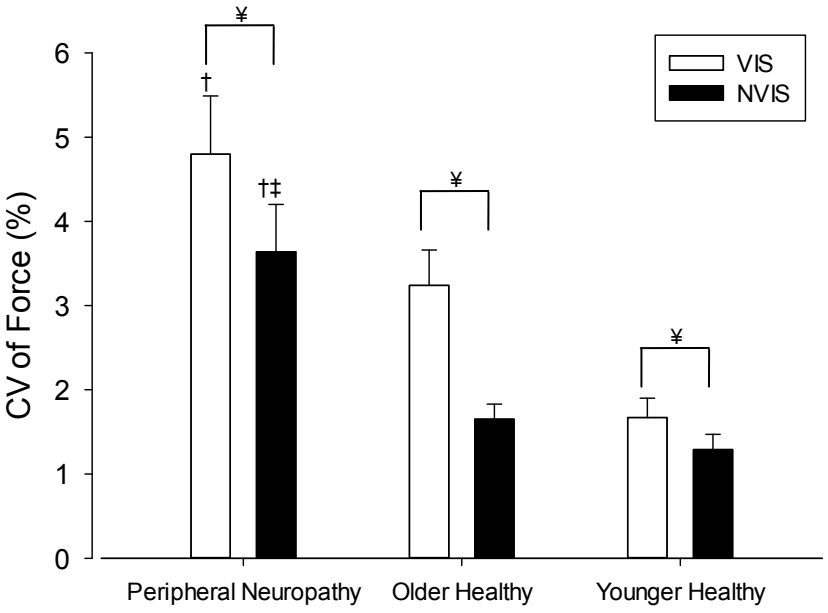


Figure 2.2A. Force Control in Plantarflexion.

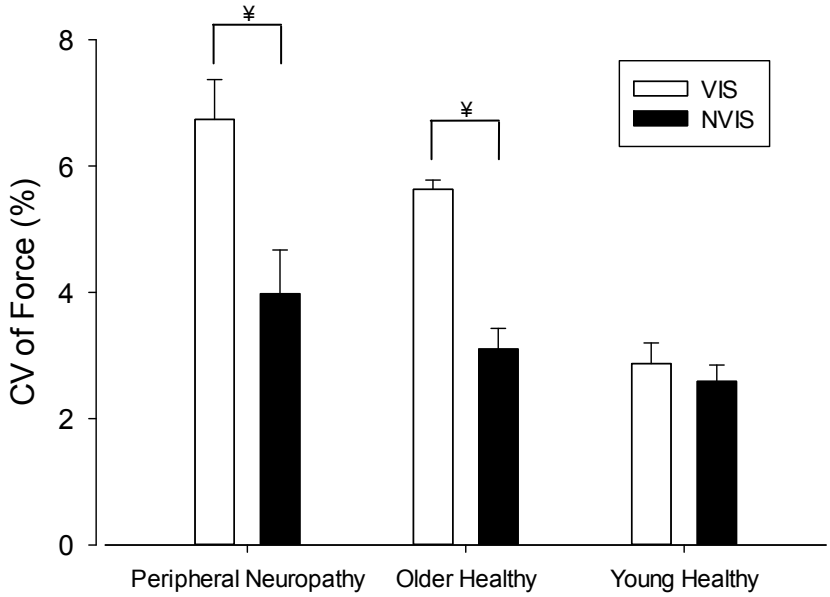


Figure 2.2B. Force Control in Dorsiflexion.

*P ≤ 0.05, O vs. Y

†P ≤ 0.05, O-PN vs. Y.

‡P ≤ 0.05, O-PN vs. O

¥ P ≤ 0.05, VIS vs. NVIS

Figure 2.2. Force Control. CV of force in DF with VIS was different ($P < 0.01$) from NVIS in neuropathy patients. CV of force in PF with VIS was different ($P = 0.03$) from NVIS in neuropathy patients. CV of force in DF with VIS was different ($P = 0.03$) from NVIS in O with NVIS. CV of force in PF with VIS was different ($P < 0.01$) from NVIS in O. CV of force in PF with VIS was different ($P = 0.05$) from NVIS in Y with NVIS. A difference existed in PF with VIS between O-PN and Y ($P < 0.01$). A difference in PF with NVIS existed between O-PN and O ($P < 0.01$) and Y ($P < 0.01$).

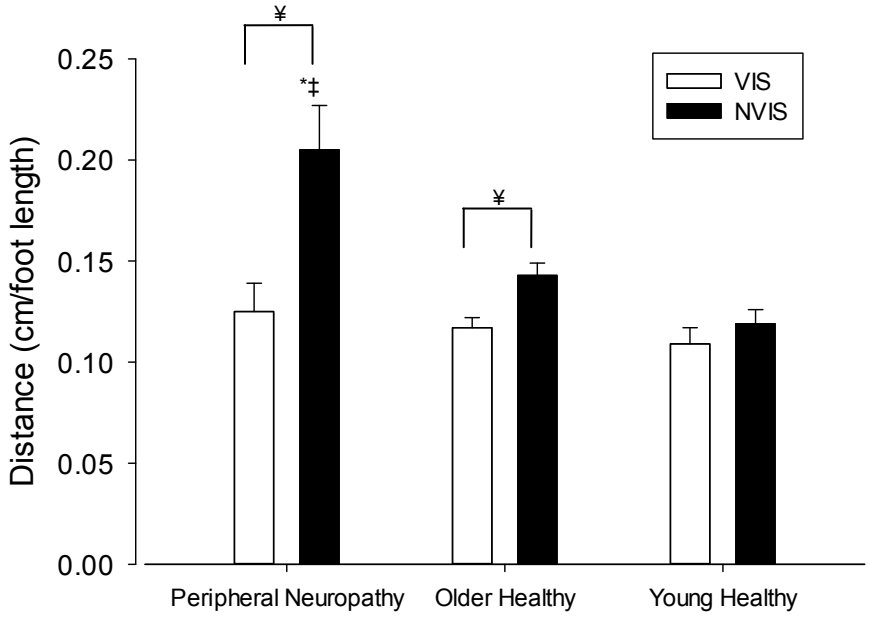


Figure 2.3A. Postural Sway.

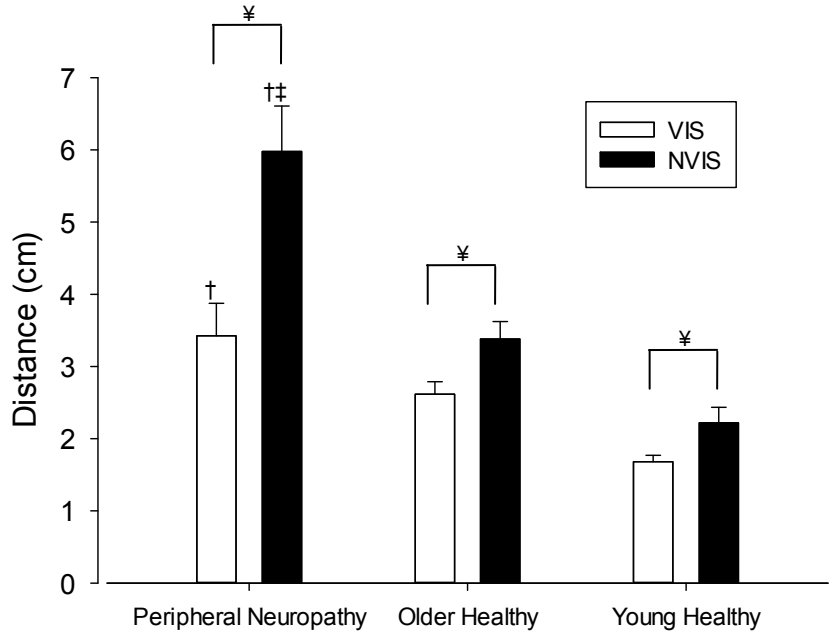


Figure 2.3B. Path Length.

*P ≤ 0.05, O vs.Y

†P ≤ 0.05, O-PN vs. Y

‡P ≤ 0.05, O-PN vs. O

¥ P ≤ 0.05, VIS vs. NVIS

Figure 2.3. Postural Steadiness. PS with VIS was different ($P < 0.01$) in neuropathy patients. PL with VIS was different ($P < 0.01$) from NVIS (5.98 ± 0.633 cm/foot length) in neuropathy patients. PS with VIS was different ($P < 0.01$) from NVIS in O. PL with VIS was different ($P < 0.01$) from NVIS in O. PS with VIS was not different ($P = 0.16$) from NVIS in Y. PL with VIS was different ($P = 0.01$) from NVIS in Y. A difference in PS with NVIS existed between O-PN and O ($P = 0.01$) and upon comparison of O-PN to Y ($P = 0.01$). A difference in PL with NVIS existed between O-PN and O ($P < 0.01$) and Y ($P < 0.01$).

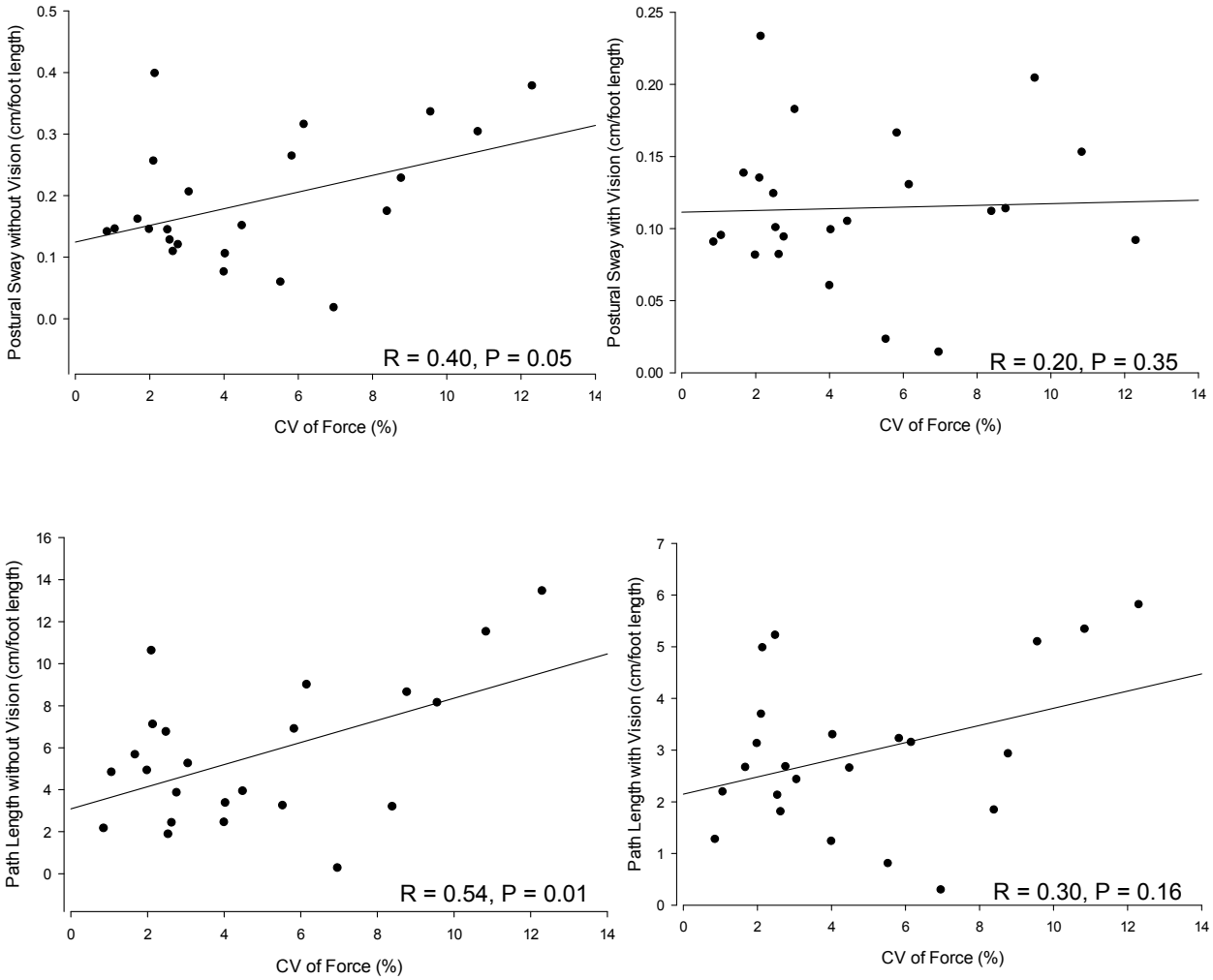


Figure 2.4. Plantarflexion Force Steadiness (No Vision)/Postural Stability Correlations in Peripheral Neuropathy Subjects.

In O-PN, correlations existed between PF force steadiness without vision in and anterior-posterior PS without vision and anterior-posterior PL without vision.

CHAPTER III – MANUSCRIPT III

Cortical and behavioral effects of rTMS in combination with constraint induced therapy in survivors of stroke

Summary

Objective: The primary objective was to compare alterations in intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI) subsequent to ten sessions of constraint induced therapy in combination with repetitive transcranial magnetic stimulation (CITrTMS) or sham rTMS (CITsham) in survivors of stroke. A second objective was the comparison of alterations in behavioral assessment scores in the between rTMS and sham rTMS. Methods: Fourteen stroke survivors were randomized into CITrTMS or CITsham (control) conditions. Measures of SICI and ICF, and physical function were assessed at baseline and after a two consecutive business weeks of intervention, and again four months following the intervention. Results: The hypotheses that while each intervention would enhance ICF (as determined by paired-pulse TMS), these enhancements would be greater in the CITrTMS group was supported. Contra to our hypothesis, SICI increased in CITrTMS. The second aim of this study was to compare alterations in behavioral measures subsequent to interventions consisting of CITrTMS and CITsham. The second hypothesis, that while each intervention would enhance functional ability, these enhancements would be greater in the CITrTMS group, was largely unsupported. Conclusions: CITrTMS enhanced cortical excitability to a greater degree than CITsham. Physical function scores, indicative of performance in

activities of daily living, were enhanced in both groups, suggesting either intervention may be suitable for enhanced rehabilitation of survivors of stroke.

Introduction

Stroke, a leading cause of long-term adult disability in the United States[155], often results in neuromuscular dysfunction of the upper limb.[156] This dysfunction reduces independent performance of activities of daily living[157] which, in turn reduces quality of life in survivors of stroke. Stroke rehabilitation techniques must be enhanced to afford a greater quality of life to survivors of stroke, as conventional modes of stroke rehabilitation typically yield only modest gains in upper extremity function.[158]

A promising mode of stroke rehabilitation is constraint-induced therapy (CIT).[159] This technique focuses treatment on the hemiparetic upper limb[160] by restraint of the non-paretic limb during training, thereby influencing the lesion-affected areas of the brain in survivors of stroke.[161] This treatment counteracts the common occurrence of learned nonuse of the hemiparetic limb in survivors of stroke.[162] CIT has been shown to improve motor function in this population as demonstrated by improved multi-joint hemiparetic upper extremity movement capacity[163] as assessed by the Wolf Motor Function Test (WMFT) and increased real-world use of the paretic upper extremity[163] as assessed by the Motor Activity Log (MAL).[164-166] These functional increases are likely due to an increase in area of the cortical representations of the hemiparetic upper extremity, as assessed by transcranial magnetic stimulation (TMS) mapping,[161] due to the correlation of the area of cortical representation and the degree of precise control of a muscle group.[167] Combining these behavioral and neural findings with the notion that the area of cortical representation is related to the degree of neuromuscular control,[168]

two observations arise. First, learned nonuse subsequent to stroke likely leads to a decreased size of motor cortical representation at the lesion-affected hemisphere with a concurrent increased area of cortical representation at the lesion-unaffected hemisphere.[161] Secondly, training of the lesion-affected upper limb leads to an enhanced area of cortical representation for the musculature of focus.[161] Taken together, these observations implicate underlying neural mechanisms leading to enhanced motor function in CIT.

A currently understudied neural aspect of rehabilitation is that of cortical excitability, which allows for neuromuscular control[169] as well as acquisition of motor skills.[170] Cortical excitability could yield insight into the central effects rehabilitation, which would allow for insight into the mechanism by which a method of rehabilitation works.[171] This insight, in turn, could allow for the design and/or refinement of rehabilitation techniques. One side of the balance of cortical excitability is intracortical facilitation (ICF), which represents the activity of cortical excitatory neurons through activity at glutamatergic synapses.[172] The other side of this balance is short-interval intracortical inhibition (SICI), which is representative of the activity of GABAergic inhibitory interneurons.[172] Previous investigations relating the role of cortical excitability to neuromuscular control in survivors of stroke have yielded important findings. Cortical excitability is lesser one week post-stroke when survivors of stroke are compared to individuals not affected by stroke.[173] Furthermore, cortical excitability and motor function are correlated in survivors of stroke.[174] What remains unknown, however, is how ICF and SICI are affected by specific, novel rehabilitation methods. A shift in ICF/SICI balance is potentially important as this could be a mechanism of enhanced

neuroplasticity[172] whereby interneural communication is altered by variation of excitatory neuron and/or inhibitory interneuron action. A shift in favor of ICF in the ICF/SICI balance would be expected to be correlated with enhanced neuromuscular function as excitatory neural outflow is the initiator of voluntary physical action.

The neurogenic mechanism of action of CIT suggests that pairing CIT with a direct intervention at the level of the motor cortex may lead to greater enhancement of functional outcomes.[175] Repetitive TMS (rTMS) has the potential to non-invasively augment cortical excitability[176] and may have the ability to act as an adjuvant treatment to CIT. Malcolm et al. demonstrated that rTMS in combination with a home-therapy program enhanced motor cortex excitability in the lesion affected hemisphere, but was minimally better than home therapy in combination with sham stimulation in improving motor function.[177] One conclusion of this investigation was that structured therapy, supervised by a therapist, is necessary to capitalize on the neurophysiological effects of rTMS.[177]

The current study examined the effect of high frequency rTMS (hereafter referred to as rTMS) in combination with CIT, on cortical and behavioral measures in survivors of stroke. The broad hypothesis of this study was that survivors of stroke receiving rTMS in combination with CIT (CITrTMS) would demonstrate greater increases in ICF, greater decreases in SICI, and greater behavioral enhancement as compared to survivors of stroke receiving sham rTMS in combination with CIT (CITsham).

Methods

Subjects. Fourteen (9 women, 5 men) survivors of ischemic stroke (mean age 63 ± 3 years, range 40 – 82 years; mean time post-stroke 27 ± 6 months, range 9 – 80 months) volunteered for participation in this study (Table 3.1). Subjects were screened for eligibility by health history questionnaire, Mini Mental Status Examination,[178] movement evaluation, electroencephalogram (EEG), and magnetic resonance image (MRI) of the brain. Both the EEG and the MRI were assessed by a board-certified neurologist for the purposes of participant safety. All participants provided written informed consent and all study procedures met the approval of the local Institutional Review Board.

Assessment. All participants underwent three identical assessment sessions. These were performed 2 days pre-intervention, two days post-intervention, and at a four months post-intervention followup (Figure 3.1). During each of these sessions, subjects underwent both cortical and behavioral evaluation. Cortical evaluation was performed using a Magstim BiStim^2 (Magstim Ltd., Carmarthenshire, UK) magnetic stimulator in conjunction with a 70 mm figure-of-eight shaped coil with the handle parallel to the subjects' sagittal plane. Subjects were placed in a semi-recumbent position while the hemiparetic arm was supported with both the shoulder and the elbow in slight flexion. Electrodes were placed in belly-tendon configuration to record surface electromyogram (sEMG) activity at the first dorsal interosseous (FDI), abductor pollicis brevis, and extensor digitorum communis muscles. sEMG activity was monitored online (Viking Select, Nicolet Biomedical, Madison, WI, USA) and recorded for subsequent offline

analysis. Motor threshold (MT) at rest was determined by varying the magnetic intensity (less intense to more intense) and was defined as the intensity at which a ~100 microvolt amplitude motor evoked potential (MEP) was elicited from FDI subsequent to 3 of 6 stimuli.[167] TMS hotspot was defined as the location at which the sEMG peak-to-peak amplitude response to magnetic stimulation was maximized in the FDI. This location was marked on a form-fitting cap. The center of the figure-of-eight coil overlaid the hotspot (approximately C3 or C4 in the international EEG 10/20 system -20% of the tragus-tragus circumference lateral to the scalp vertex along the coronal line). The hotspot location was recorded as the lateral distance from the vertex of the skull and the anterior/posterior distance from the inter-aural line to ensure consistent TMS coil placement between assessment sessions. 40 TMS stimuli were provided in randomized order and included a conditioning stimulus (CS; 90% MT), test stimulus (TS; 116% MT), SICI (CS followed by TS at 2 ms), and ICF (CS followed by TS at 15 ms). Peak-to-peak amplitude was assessed for each stimulus. A minimum of six seconds were provided between each stimulus. Participants were fitted with hearing protection for the duration of all TMS sessions.

The Motor Activity Log (MAL), Stroke Impact Scale (SIS) and Wolf Motor Function Test (WMFT) were performed as described previously.[179-182] Briefly, the MAL is an instrument utilized to determine real-world use of the upper limb as well as an individual's perceptions of said function, making it a key indicator of stroke recovery. A uniform set of questions was asked of each participant. These questions allow for rating a survivor of stroke in the areas of number of activities attempted as well as average rating of how well attempted activities were performed. The MAL has been shown to be

both reliable and valid.[183] The SIS is an instrument used to assess stroke recovery from the perspectives of physical function, emotional and psychological health as well as social function. A uniform set of questions (including the areas of strength, hand function, mobility, activities of daily living, emotion, memory, communication and social participation) was asked of each participant. Both the SIS and the MAL require a trained interviewer and a standardized manner of execution. In the WMFT, a series of physical tasks are performed to determine the degree of upper extremity dexterity, strength and function that an individual possesses. While the time and strength components of this assessment are objective, a trained assessor must be present to perform movement analyses where scores may range from “does not attempt with the involved arm” to “arm does participate; movement appears to be normal.” The WMFT has been shown to be both internally consistent and reliable.[184]

Intervention

Participants were randomized to one of two groups, the first of which received rTMS immediately prior to each CIT training session (CITrTMS). The second group received sham rTMS prior to each training session (CITsham).

During treatment, an identical sEMG electrode configuration was used as that found in the assessment sessions with the addition of electrodes placed over the biceps brachii for the monitoring of a potential spread of sEMG activity, as visualized online, indicative of concurrent spread of cortical hyperexcitability associated with seizure during rTMS.[185] If a spread of cortical hyperexcitability was present, it would be mirrored by monitoring the sEMG of a variety of cortically discrete muscle groups. On the first

day of the intervention, hotspot location and MT were determined in both the CITrTMS and CITsham groups over the lesion affected motor cortical representation of FDI. Measurements of hotspot and MT collected during the assessment session could not be used for administration of rTMS as a different stimulator and coil were used during treatment. While the hotspot location recorded on the first day of intervention would be used for the ten subsequent treatment sessions, MT was determined daily to account for any day-to-day fluctuations in MT. The magnetic stimulator (Magstim Rapid 2, Magstim, Carmarthenshire, UK) was set to an intensity of 90% MT. 1600 stimuli were delivered over the course of approximately twenty minutes on each treatment day (40 trains, 20 Hz stimulation frequency, 2 second duration, 28 second intertrain interval). An air-cooled 70 mm figure-of-eight coil was used in the CITrTMS group while a visually identical sham coil was used in the CITsham group whereby the mechanical and aural sensory cues associated with rTMS were present with no concurrent magnetic stimulation.

Both CITrTMS and CITsham groups received five hours of CIT immediately post rTMS/sham administration during each treatment session. Participants wore a restraining mitt on the non-hemiparetic hand for the duration of daily training, which included functional tasks (e.g. cooking, writing, puzzle solving). During the two weeks of treatment (including the intervening weekend), participants were provided with a restraining mitt for use offsite and were requested to wear the mitt on the non-hemiparetic hand for ≥90% of waking hours. The remaining 10% of waking hours were deemed adequate for activities not suited to the mitt (e.g. shaving, showering).

Data Treatment and Statistical Analysis.

The ratio of each individual SICI and ICF amplitude value to the average TS amplitude value was calculated for every assessment session to identify the degree of inhibition and facilitation present, while controlling for inter-assessment baseline cortical excitability variability. Only data collected from the FDI is presented herein as that was the cortical representation utilized for hotspot and MT determination during rTMS and ppTMS.

All statistical analyses were performed in IBM SPSS Statistics 21 (Chicago, IL). For all measures with the exception of the MAL, a 2 x 3 mixed design analysis of variance was used to assess main effects of treatment (CITrTMS, CITsham), time (pre-treatment, post-treatment and 4-month followup), and time by treatment interactions. *Post hoc t*-tests were performed where appropriate. For the MAL, the Mann-Whitney test was applied to determine between-group differences and the Friedman test was used to determine within-group differences with Kruskal-Wallis *post hoc* tests performed where appropriate. Alpha (α) was set to 0.05. All values are presented as mean ± standard error.

Results

CIT was well tolerated by all subjects as were TMS, rTMS and sham rTMS. No adverse events were associated with this investigation.

TMS Outcomes

Motor Threshold

No baseline difference in motor threshold between groups existed (t = 0.550, p = 0.59). No alterations in motor threshold were detected as a main effect of time ($F_{(2,22)}$ = 0.129, p=0.88), CITrTMS (pre-: 68.9 ± 6.9, post-treatment: 69.43 ± 6.2, followup: 67.6 ± 6.7) CITsham (pre-: 64.8 ± 7.4, post-treatment: 62.7 ± 6.7, followup: 63.7 ± 7.2)) nor was a time by treatment interaction present ($F_{(2,22)}$ = 0.218, p=0.81).

Intracortical Inhibition

SICI was greater in the CITrTMS group at baseline (t = 3.996, p < 0.01) as compared to CITsham. The results of the SICI outcomes are displayed in Figure 3.2. SICI was found to be enhanced (reflected as lesser values) as a main effect of time for FDI ($F_{(2,154)}$ = 5.960, p < 0.01) (CITrTMS (pre-: 1.10 ± 0.17, post-treatment: 0.61 ± 0.40, followup: 0.52 ± 0.07), CITsham (pre-: 0.41 ± 0.06, post-treatment: 0.38 ± 0.05, followup: 0.40 ± 0.11)) with a time by treatment interaction ($F_{(2,154)}$ = 5.428, p < 0.01). CITrTMS differed between pre- and post-treatment (t = 2.404, p = 0.03) as well as pre-treatment and followup (t = 2.448, p = 0.02).

Intracortical Facilitation.

ICF was greater in the CITrTMS group at baseline (t = 2.209, p = 0.03) as compared to that of the CITsham group. The results of the ICF outcomes are displayed in Figure 3.3. ICF was enhanced as a main effect of time for FDI ($F_{(2,156)}$ = 7.083, p < 0.01) (CITrTMS (pre-: 1.83 ± 0.29, post-treatment: 2.98 ± 0.36, followup: 2.39 ± 0.29), CITsham (pre-: 1.25 ± 0.23, post-treatment: 1.22 ± 0.12, followup: 1.03 ± 0.20)) with significant

differences between pre- and post-treatment *(t* = 2.296, *p* = 0.02) as well as post-treatment and followup *(t* = 2.059, *p* = 0.04). A time by treatment effect was also present ($F_{(2,156)}$ = 7.666, *p* < 0.01). FDI ICF in CITrTMS was significantly enhanced at post- compared to pre-treatment (*t* = 4.654, *p* < 0.01). FDI ICF in CITsham was different upon comparison of pre-treatment to followup (*t* = 2.432, *p* = 0.18).

Functional Outcomes

Wolf Motor Function Test

No baseline difference in mean affected time existed between groups (*t* = 0.885, *p* = 0.39). A main effect of time was detected in mean time of the hemiparetic limb ($F_{(2,26)}$ = 5.689, *p* < 0.01) (CITrTMS (pre-: 41.41 ± 12.20, post-treatment: 36.09 ± 12.38, followup: 33.31 ± 11.76), CITsham (pre-: 57.90 ± 13.77, post-treatment: 45.83 ± 13.37, followup: 47.10 ± 14.31)). Significant differences were found between pre- and post-assessment *(t* = 2.397, *p* = 0.03) as well as pre-assessment and followup (*t* = 2.771, *p* = 0.02). No time by treatment interactions were present ($F_{(2,26)}$ = 0.595, *p* = 0.56).

No baseline difference in mean functional ability existed between groups (*t* = 0.637, *p* = 0.54). A main effect of time was detected in mean functional ability ($F_{(2,26)}$ = 9.054, *p* < 0.01) (CITrTMS (pre-: 2.44 ± 0.29, post-treatment: 2.76 ± 0.34, followup: 2.86 ± 0.36), CITsham (pre-: 2.13 ± 0.38, post-treatment: 2.32 ± 0.38, followup: 2.34 ± 0.39)). Significant differences were found between pre- and post-assessment *(t* = 2.617, *p* = 0.02) as well as pre-assessment and followup *(t* = 3.679, *p* < 0.01). No time by treatment interactions were present ($F_{(2,26)}$ = 0.887, *p* = 0.42).

Stroke Impact Scale

No baseline difference in percentage recovery existed between groups (t = 0.079, p = 0.94). A main effect of time was detected in percentage recovery ($F_{(2,26)}$ = 15.021, p < 0.01) (CITrTMS (pre-: 37.86 ± 8.15, post-treatment: 49.29 ± 11.15, followup: 52.86± 11.54), CITsham (pre-: 38.75 ± 7.83, post-treatment: 51.86 ± 9.35, followup: 58.13 ± 7.67)). Significant differences were found between pre- and post-assessment *(*t = 4.281, p < .01) as well as pre-assessment and followup *(*t = 4.630, p < 0.01). No time by treatment interactions were present ($F_{(2,26)}$ = 0.323, p = 0.58).

No baseline difference in overall average existed between groups (t = 1.091, p = 0.39). A main effect of time was detected in overall average score ($F_{(2,26)}$ = 4.840, p = 0.30) (CITrTMS (pre-: 4.13 ± 0.18, post-treatment: 4.35 ± 0.22, followup: 4.21 ± 0.23), CITsham (pre-: 3.92 ± 0.09, post-treatment: 4.14 ± 0.13, followup: 4.08 ± 0.14)). Significant differences existed between pre- and post-assessment *(*t = 3.299, p < 0.01). No time by treatment interactions were present ($F_{(2,26)}$ = 0.389, p = 0.54).

Motor Activity Log

For the number of activities performed, no between-group differences existed at pre- (Z = 1.450, p = 0.15), post-assessment (Z = 0.815, p = 0.46) or followup (Z = 1.394, p = 0.19). For CITrTMS, a main effect of time existed for the number of activities performed ($\chi^2_{(2)}$ = 7.630, p = 0.02) (pre-: 18.57 ± 2.59, post-treatment: 23.43 ± 2.21, followup: 22.14 ± 2.67). *Post hoc* tests revealed a significant increase from pre- to post-treatment (Z = 2.214, p = 0.02) and from pre-treatment to followup (Z = 2.124, p = 0.03), and no significant change from post-treatment to followup (Z = 1.190, p = 0.23). For CITsham,

the number of activities performed was affected by time ($\chi^2_{(2)}$ = 10.516, p = 0.01) (pre-: 13.25 ± 2.48, post-treatment: 20.50 ± 2.41, followup: 17.88 ± 2.62). *Post hoc* tests revealed a significant increase from pre- to post-treatment (Z = 2.103, p = 0.04) and from pre-treatment to followup (Z = 2.530, p = 0.01), and a no significant change from post-treatment to followup (Z = 1.1357, p = 0.18).

For the average rating of activities performed, as represented in Figure 3.4, no between-group differences existed at pre- (Z = 0.463, p = 0.69), post-assessment (Z = 0.174, p = 0.87) or followup (Z = 0.811, p = 0.463). For CITrTMS, an effect of time existed for the number of activities performed ($\chi^2_{(2)}$ = 11.143, p < 0.01) (pre-: 2.35 ± 0.21, post-treatment: 3.18 ± 0.30, followup: 3.30 ± 0.44). *Post hoc* tests revealed a significant increase from pre- to post-treatment (Z = 2.366, p = 0.02) and from pre-treatment to followup (Z = 2.366, p = 0.02), and no significant change from post-treatment to followup (Z = 0.507, p = 0.61). For CITsham, the average rating of activities performed was affected by time ($\chi^2_{(2)}$ = 7.750, p = 0.02) (pre-: 2.66 ± 0.37, post-treatment: 3.25 ± 0.32, followup: 2.85 ± 0.43). *Post hoc* tests revealed a significant increase from pre- to post-treatment (Z = 2.521, p = 0.01) and from pre-treatment to followup (Z = 1.960, p = 0.05), and no significant change from post-treatment to followup (Z = 0.980, p = 0.33).

Discussion

Enhanced modes of stroke treatment are necessary so as to better equip the clinician in facilitating as full a recovery as possible in survivors of stroke. To this end, a more complete picture of physical, behavioral and neural outcomes must be gained. The

present investigation addressed this need through the investigation of the therapeutic potential of a novel post-stroke intervention (CITrTMS).

We aimed to assess alterations in cortical excitability subsequent to interventions consisting of CIT plus rTMS and CIT plus sham rTMS. While ICF was enhanced in both group, CIT plus rTMS provided greater enhancement than CIT plus sham rTMS. Contra to our hypothesis, SICI increased. The second aim of this study was to compare alterations in behavioral measures subsequent to interventions consisting of CIT plus rTMS and CIT plus sham rTMS. The second hypothesis, that while each intervention would enhance functional ability, these enhancements would be greater in the CITrTMS group, was largely unsupported.

Cortical Excitability

The motor cortex is overtly involved in control of all voluntary movement.[186] As such, cortical excitability is thought to be related to functional ability.[187] Cortical excitability is governed by two uniquely opposed influences: facilitation and inhibition.[188] At the level of the motor cortex, these counteracting forces influence the likelihood of downstream neural activity,[188] which influences the likelihood of meaningful voluntary movement.[186] Increasing the likelihood of cortical excitatory neuron discharge is likely to enhance neuroplasticity.[172]

Previous studies investigating the effect of high-frequency rTMS on cortical excitability have met with mixed results in regard to cortical inhibition. For example, Di Lazzaro et al. found a decrease in intracortical inhibition five minutes post high frequency rTMS train,[189] while Peinemann et al. found no change in intracortical

inhibition immediately following a train of high frequency rTMS.[190] Results of the present investigation are opposed to these previous findings in that cortical inhibition was found to be increased following the intervention. Three key elements separate the current study from those performed previously. The post-treatment measurement of cortical inhibition occurred two days after the cessation of treatment. Inhibitory interneurons could potentially be affected by the high frequency rTMS and, in turn, experience a "rebound" post-treatment whereby their action was enhanced. Furthermore, the current intervention provided ten doses of high frequency rTMS over the course of as many days. The profundity of this difference in amount of treatment could account for differences in outcomes of this study as compared to previous studies. A third and final key difference, which could potentially be of the greatest import, is that of combining high frequency rTMS and CIT. In short, CIT affects the areas of the motor cortex influenced and examined by TMS[161] and could, therefore, directly influence inhibitory signaling.

Previous studies investigating the effect of high frequency rTMS on cortical facilitation have provided mixed results, as well. While a variety of studies, including those performed by Lefaucheur et al. have shown high frequency rTMS to provide no influence on cortical facilitation[191] other studies, such as that performed by Wu et al., have found high frequency rTMS to enhance cortical facilitation.[192] These latter findings may be more similar to those of the present study secondary to a more similar nature of the intervention.

Functional Ability

Enhanced functional ability is the end-goal as well as the criterion by which most rehabilitative interventions for stroke survivors are judged. CIT in survivors of stroke has proven to be quite effective from this perspective.[182] Though physical conditioning including strength and endurance are typically improved by stroke treatment regimens, CIT is uniquely powerful in that it facilitates both positive behavioral and neurophysiological alterations. The findings of the present study mirror those found previously in that functional scores are significantly enhanced in stroke patients subsequent to CIT.[182] Though the addition of rTMS provided little acute functional advantage over CIT alone (as assessed by pre- vs. post-treatment comparison), the lasting benefits, particularly in terms of trends found in MAL, demonstrate a potential advantage of the combined treatments. Furthermore, the increased ICF conferred by the addition of rTMS to CIT could be explanative regarding potentially enhanced long-term functional improvements.

Previous studies investigating the effect of high frequency rTMS on functional ability have met with mixed results. Benninger et al. found chronic application of high frequency rTMS to the motor cortices of Parkinson's Disease patients to not improve scores on the Unified Parkinson's Disease Rating Scale assessment.[193] Though not directly related to the condition of stroke, these findings may be similar to those of sub-cortical stroke in the thalamic region of the brain. A study more similar in design to the present investigation was performed by Chang et al. in 2010.[194] Though both rTMS and sham rTMS treatments were shown to improve scores on the Motoricity Index, a time by treatment interaction was present in which rTMS improved scores to a greater

degree.[194] These findings are most similar to those of the present study in that MAL score improvement trend suggests greater persistence with the combination of rTMS and CIT as opposed to CIT alone.

The generalizability of this study could be enhanced by the addition of participants suffering from hemmhoragic stroke. Though the underlying nature of stroke types is different, the outcomes (both at the level of the brain and functionality) are similar. Finally, the present study may suffer from the level of accuracy of the functional outcome measures collected. Kinematic analyses of the CITrTMS intervention could potentially enhance further comparison to CITsham. In spite of this, the present results are likely most meaningful and applicable to the clinical environment were the MAL and WMFT are often used to gauge both baseline and post-treatment outcomes in stroke.

Conclusion

The present study found SICI and ICF to be enhanced in response to both CITsham and CITrTMS, though the increase in ICF was greater in the CITrTMS group. Several of these increases were shown to persist for up to four months post-treatment. CITsham and CITrTMS were both found to improve functional ability.

Tables

Table 3.1. Subject Characteristics.

Participant	Group	Sex	Age (years)	Stroke to Treatment (months)	CVA Hemisphere	Stroke Location
1	CITsham	Female	56	65	right	subcortical
2	CITsham	Female	51	12	right	subcortical
3	CITrTMS	Female	66	80	right	subcortical
4	CITrTMS	Male	70	12	right	subcortical
5	CITsham	Male	82	22	right	subcortical
6	CITrTMS	Female	71	38	right	subcortical
7	CITrTMS	Female	40	12	left	cortical
8	CITrTMS	Male	57	20	left	cortical
9	CITsham	Male	72	24	left	brainstem
10	CITrTMS	Female	61	12	left	subcortical
11	CITsham	Female	47	16	left	cortical
12	CITsham	Female	61	9	right	subcortical
13	CITsham	Female	77	59	right	brain stem
14	CITrTMS	Male	62	14	left	cerebellum

Figures

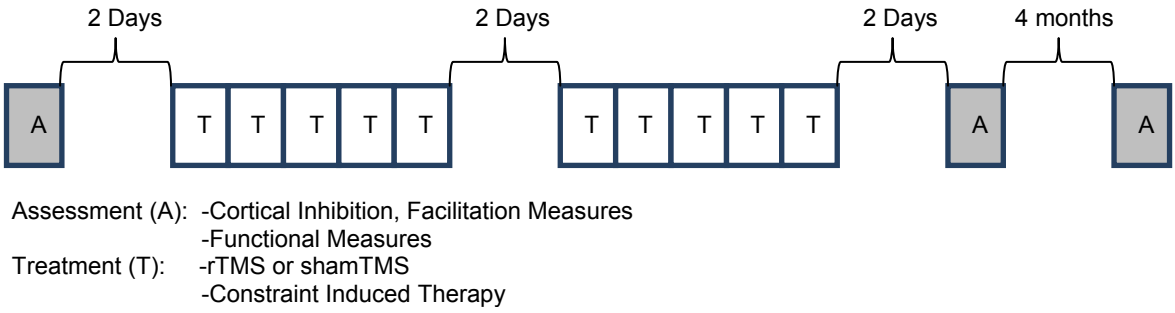
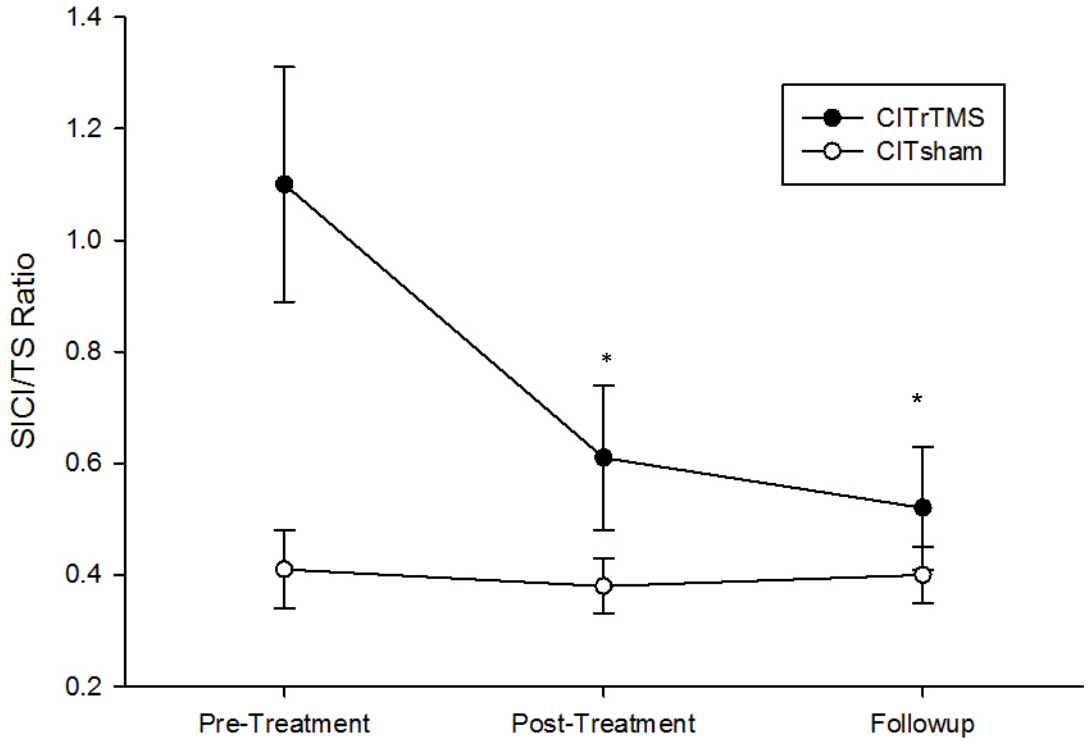
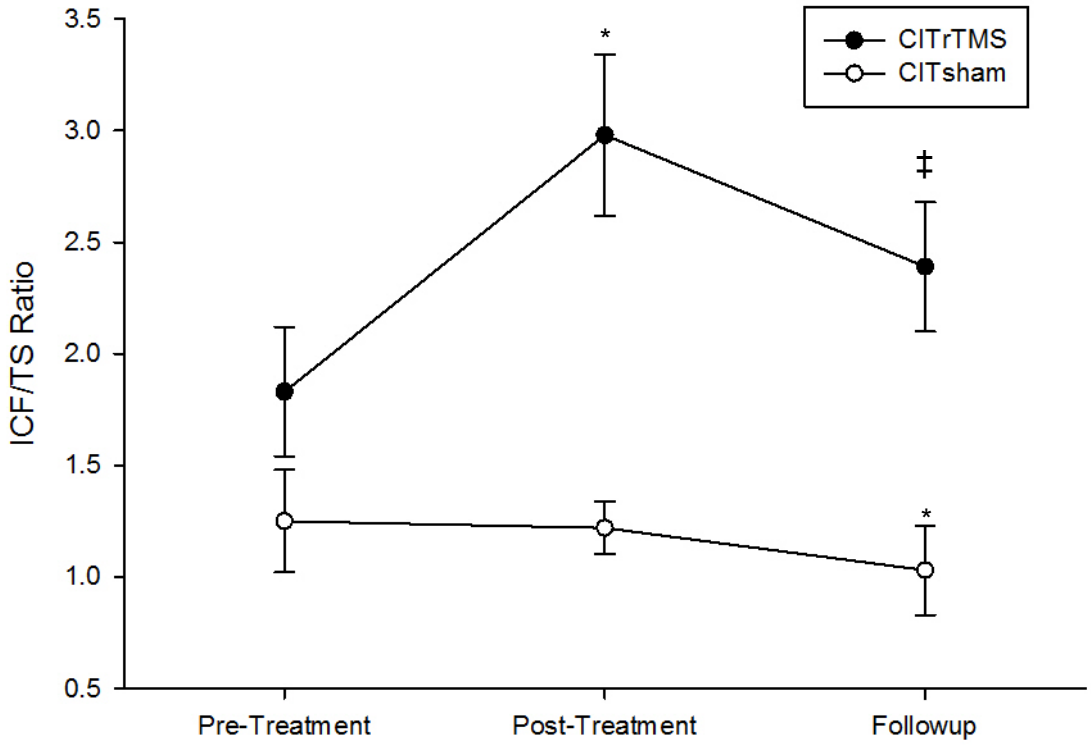


Figure 3.1. Timeline. Schematic representation of the series of visits for each subject.



*CITrTMS SICI greater than pre-treatment ($p < 0.05$)

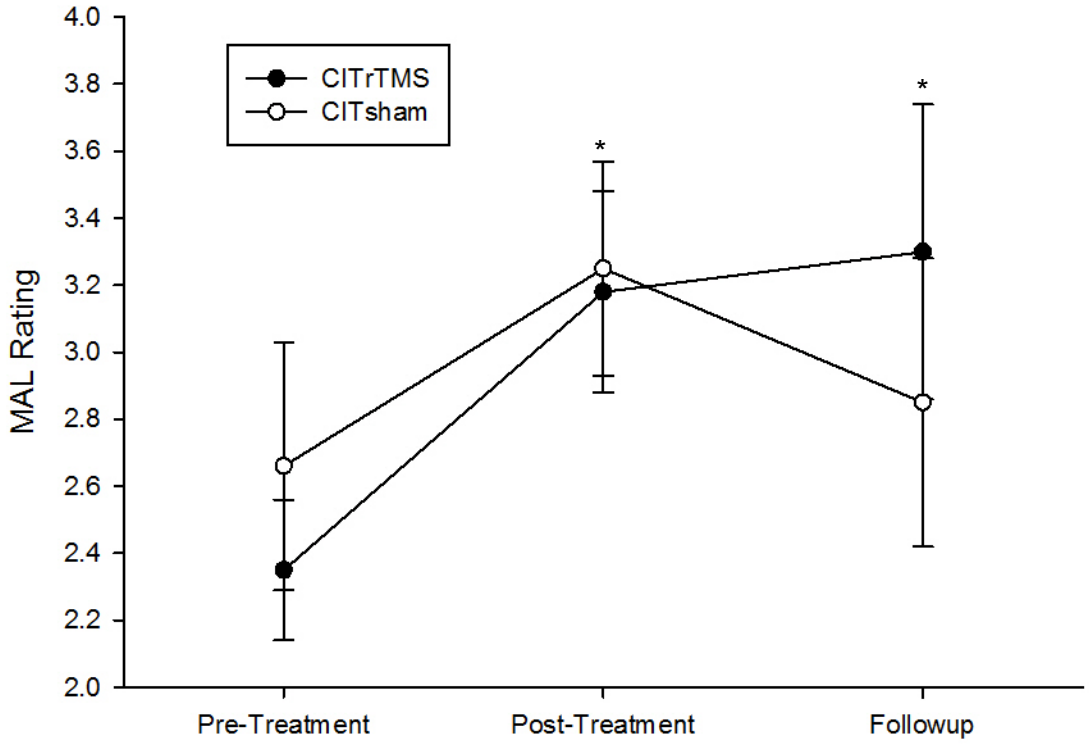
Figure 3.2. SICI/TS Ratio. SICI was found to be enhanced (reflected as lesser values) as a main effect of time with a time by treatment interaction. CITrTMS differed between pre- and post-treatment as well as pre-treatment and followup.



*Differs from pre-treatment ($p < 0.05$)

‡Differs from post-treatment ($p < 0.05$)

Figure 3.3. ICF/TS Ratio. ICF was enhanced as a main effect of time for FDI with significant differences between pre- and post-treatment as well as post-treatment and followup. A time by treatment effect was also present. FDI ICF in CITrTMS was significantly enhanced at post- compared to pre-treatment. FDI ICF in CITsham was different upon comparison of pre-treatment to followup.



*Differs from pre-treatment in both groups ($p < 0.05$)

Figure 3.4. MAL Average Rating of Activities Performed. The average rating of activities performed was enhanced as main effect of time with significant differences between pre- and post-treatment as well as pre-treatment and followup

CHAPTER IV – MANUSCRIPT IV

Long-term cortical and behavioral alterations subsequent to functional repetitive transcranial magnetic stimulation in survivors of stroke

Summary

Objective: The primary objective was to compare alterations in intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI) subsequent to eight sessions of functional repetitive transcranial magnetic stimulation (rTMS) or passive rTMS in survivors of stroke. A second objective was the comparison of alterations in behavioral assessment scores in the between functional rTMS and passive rTMS. Methods: Twenty-one stroke survivors were randomized into functional-rTMS (EMG-triggered rTMS) or passive-rTMS (rTMS only; control) conditions. Measures of SICI and intracortical facilitation ICF, and physical function were assessed at baseline and after two sessions of rTMS per day for four consecutive workdays, and again four weeks following the intervention. Functional-rTMS required subjects to exceed a muscle activation threshold assessed by surface electromyography to trigger each rTMS train; the passive-rTMS group received rTMS while relaxed. Results: Functional rTMS increased cortical excitability to a greater degree than passive rTMS. SICI remained unaltered in both groups. Although both groups' behavioral scores improved in some metrics, neither intervention proved superior. Conclusions: The functional rTMS protocol enhanced cortical excitability to a greater degree than passive rTMS. Physical function scores, indicative of performance in activities of daily living, were enhanced in both

groups, suggesting either intervention may be suitable for enhanced rehabilitation of survivors of stroke.

Introduction

Stroke is a leading cause of long-term adult disability in the United States[155] in which neuromuscular dysfunction of the upper limb is a common sequella. This dysfunction commonly reduces independent performance of activities of daily living[157] which, in turn reduces quality of life.[157] Stroke rehabilitation techniques must be enhanced to afford a greater quality of life to survivors of stroke as conventional modes of stroke rehabilitation typically yield only mild gains in upper extremity function.[158]

Several recent studies suggest that repetitive transcranial magnetic stimulation (rTMS) may provide improved cortical and neuromuscular function in survivors of stroke.[159-161,195] rTMS provided to the lesion-affected cortex, for instance, has been shown to enhance kinematic outcomes in the case of subcortical stroke but not in cases of cortical stroke.[196] Previous studies regarding the use of rTMS as a tool for stroke rehabilitation suggests this to be a promising treatment.[197]

Several previous investigations of rTMS as a treatment for stroke have conditioned the cortex with rTMS and followed immediately with conventional treatment.[195,198-203] An alternate treatment schema whereby physiological action triggers rTMS could potentially act to bolster central nervous function. This notion is similar to studies investigating surface electromyogram (sEMG) triggered electrical stimulation of skeletal musculature with the goal of enhanced rehabilitation.[204,205] sEMG triggered treatment has been hypothesized[205] to result in enhanced neuromuscular function,

particularly in survivors of stroke with moderate hemiparesis.[206-208] A recent systematic review of the literature suggests that though the notion of sEMG triggered treatment remains attractive, it has been found to be no more effective than standard treatment of the upper extremity[209], though this is likely due to insufficient sample sizes and/or interindividual study participant variability.[209] In spite of this lack of difference, functional magnetic resonance imaging studies have shown that sEMG triggered electrical stimulation to increase neuroplasticity[204,210], presumably by the addition of a cognitive component of the treatment. This suggests that an sEMG triggered intervention administered at the brain and known to enhance neuroplasticity[211] could be an appealing alternative. The present study aimed to investigate outcomes of rTMS provided concurrently with targeted, voluntary activation of the paretic hand (functional rTMS) as compared to rTMS provided with the paretic hand relaxed (passive rTMS).

Cortical excitability, as assessed by paired pulse transcranial magnetic stimulation (ppTMS), is a powerful tool for the investigation of alterations in the central nervous system secondary to rehabilitation treatments and may provide insight into the underlying mechanisms of stroke rehabilitation.[212] Cortical excitability is typically assessed by measurement of intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI).[213] ICF is thought to represent the activity of cortical pyramidal excitatory neurons through increased activity at gluraminergic synapses.[172] SICI is typically considered to be representative of increased activity of GABAergic inhibitory interneurons.[172] A shift in ICF/SICI balance is potentially important as this could be interpreted as a mechanism of enhanced neuroplasticity[172] whereby interneural communication could be altered by alteration of excitatory neuron and/or

inhibitory interneuron action. Comparing functional rTMS to passive rTMS in terms of ICF and SICI could identify which treatment allows for a greater increase in neuroplasticity and could explain why superior behavioral outcomes in one treatment as compared to the other might exist.

The first objective of the present investigation was to compare alterations in ICF and SICI subsequent to eight sessions of functional rTMS or passive rTMS in survivors of stroke. We hypothesized that functional rTMS produce greater increases in ICF and greater decreases in SICI, than passive rTMS. A second objective was the comparison of alterations in behavioral assessment scores between functional rTMS and passive rTMS. The broad hypothesis of this study was that functional rTMS would enhance behavioral outcomes to a greater degree than passive rTMS as assessed by greater increases in Fugl-Meyer, Motor Activity Log (MAL), grip strength, and Box and Block Test (BBT) scores.

Methods

Subjects

Twenty-one survivors of stroke volunteered for participation in this study (see Table 4.1 for demographic characteristics). All participants provided written informed consent and all procedures were approved by the local Institutional Review Board.

Research Setup

Subjects were randomized to functional rTMS or passive rTMS and subsequently participated in the intervention on 4 consecutive days. Briefly, subjects were seated in a

semi-recumbent position while the paretic arm was supported with both the shoulder and the elbow in slight flexion. sEMG electrodes were placed in belly-tendon configuration to record activity at the first dorsal interosseous (FDI), abductor pollicis brevis, flexor pollicis brevis, and biceps brachii muscles. sEMG activity was monitored online (PowerLab 16/30, LabChart 7.0 Pro; AD Instruments, Christchurch, New Zealand) with a sampling frequency of 2 kHz (bandpass filtered from 1 Hz – 5 kHz) during rTMS application for the monitoring of the potential spread of sEMG activity as well as post rTMS train sEMG activity, at the four muscles (indicative of concurrent spread of cortical hyperexcitability associated with seizure during rTMS).[185] rTMS was applied by use of a Magstim Rapid^2 stimulator (Magstim Ltd., Carmarthenshire, UK) in conjunction with an air-film cooled 70 mm figure-of-eight magnetic coil positioned over the hot spot for the representation of FDI, defined as the position eliciting the greatest sEMG response to supra motor threshold (MT) TMS. MT at rest was determined by varying the magnetic intensity (less intense to more intense) and was defined as the intensity that elicited a motor evoked potential (MEP) of greater than or equal to 100 microvolts from FDI subsequent to 3 of 6 TMS stimuli.[172]

Maximal voluntary contraction (MVC) force was assessed at the beginning of each intervention session during a lateral pinch task. Participants were instructed to maintain a lateral pinch on a force transducer (Transducer Techniques, Temecula, CA, USA) between the pad of the thumb and the proximal interphalangeal joint of the first digit. During MVCs, subjects were instructed to increase isometric force over approximately 3 seconds and then exert maximal force for 2 to 3 seconds[214] while exhaling and receiving strong verbal encouragement. At least three MVC trials were

performed with intervening rest intervals of one minute to decrease any potential effects of fatigue. MVC trials were performed until two trials were within five percent of one other (up to five trials were typically necessary).

Intervention stimulus intensity for rTMS was 70% of MT and was provided at 10 Hz in three second trains with thirty second inter-train intervals. Forty total trains were provided in each dose of rTMS and two doses were provided on each day of the intervention with a fifteen minute rest period between rTMS doses. Functional rTMS recipients activated each rTMS train by sEMG activity produced equal to that found at fifteen percent maximal voluntary contraction during the key grip maneuver as assessed at FDI. Passive rTMS recipients served as the control group by receiving rTMS with no concurrent muscle activation (i.e. no triggering of rTMS trains). Treatments in all subjects were provided on four consecutive business days.

Subjects participated in evaluation sessions on the business day immediately prior to, post, and 1-month post intervention. During each of these sessions, subjects underwent both cortical and behavioral evaluation. Cortical evaluation was performed using a Magstim BiStim^2 (Magstim Ltd., Carmarthenshire, UK) in conjunction with a 70 mm figure-of-eight shaped coil with the handle parallel to the sagittal plane. Hot spot and MT were determined in a manner identical to that used for rTMS. Forty-one ppTMS assessment stimuli were provided in randomized order and included a conditioning stimulus (90% MT), test stimulus (116% MT), SICI (CS followed by TS at 2 ms), and ICF (CS followed by TS at 15 ms). Peak-to-peak amplitude (AMP) was assessed for each assessment stimulus by online data collection and subsequent offline analysis utilizing the same sampling, filtering and equipment scheme as in the intervention.

The MAL and Fugl-Meyer were performed as described previously.[179-182] Briefly, the MAL is an instrument utilized to determine real-world function of the upper limb as well as an individual's perceptions of said function, making it a key indicator of stroke recovery. A uniform set of questions were asked of the participant. These questions allow for rating a stroke survivor in the areas of number of activities attempted as well as average rating of attempted activities. The MAL has been shown to be both reliable and valid[183,215]. The MAL requires a trained interviewer and a standardized manner of execution. In the Fugl-Meyer Assessment, a series of physical tasks are performed to determine the degree of recovery achieved by an individual post-stroke. A trained assessor must be present to perform movement analyses to properly assign scores. The Fugl-Meyer Assessment has been shown to be both internally consistent and reliable.[216,217] The box and block test (BBT) assessed grasp, transport and release of small objects, as previously described.[218] Performance was defined as number of blocks successfully moved in one minute. Grip strength was also assessed using an analog hand grip dynamometer.

ICF and SICI were obtained for each session by dividing the paired-pulse MEP amplitude value by the average TS MEP amplitude to identify the degree of facilitation and inhibition present, while controlling for inter-assessment baseline excitability variability.

All statistical analyses were performed in IBM SPSS Statistics 21 (Chicago, IL). A Student's *t*-test was used to assess baseline differences between treatment groups. For each measure, a 2 x 3 mixed analysis of variance (ANOVA) was used to compare effects of time (pre-treatment, post-treatment and 4-month post-treatment), treatment

(functional rTMS, passive TMS), and time by treatment interactions. *Post hoc* pairwise *t*-tests were performed where appropriate. For the MAL, the Mann-Whitney test was applied to determine between-group differences and the Friedman test was used to determine within-group differences with Kruskal-Wallis *post hoc* tests performed where appropriate. Alpha (α) was set to 0.05. All values are presented as mean ± standard error.

Results

Physiological Measures

Only data collected from the FDI is presented herein as that was the cortical representation utilized for hotspot and MT determination during rTMS and ppTMS.

An baseline between-group difference existed for ICF (t = 4.053, p < 0.01). ICF (Figure 4.1) was increased as a main effect of time ($F_{(2,376)}$ = 7.463, p < 0.01) (functional rTMS pre-: 2.6 ± 0.3, post-treatment: 3.7 ± 0.3, followup: 2.9 ± 0.2; passive rTMS pre-: 1.5 ± 0.2, post-treatment: 1.7 ± 0.1, followup: 1.4 ± 0.1) and of treatment (F(1,188) = 40.845, p < 0.01). A time by treatment interaction existed ($F_{(2,376)}$ = 3.781, p = 0.02). Mean ICF significantly increased in the functional rTMS group upon comparison of pre- to post-treatment (t = 4.373, p < 0.01) and post-treatment to followup (t = 2.166, p = 0.03) while no significant difference was noted between pre-treatment and followup (t = 0.162, p = 0.87). No significant differences between assessments were observed in the passive rTMS group upon comparison of pre- to post-treatment (t =1.065, p = 0.29), pre-treatment to followup (t = 0.608, p = 0.55), and post-treatment to followup (t = 0.984, p = 0.33).

No baseline between-group difference existed for SICI (t = 1.498, p = 0.14). SICI, as represented by FDI amplitude, remained unaltered as a main effect of time by functional rTMS or passive rTMS ($F_{(2,542)}$ = 0.889, p = 0.41) (functional rTMS pre-: 0.8 ± 0.1, post-assessment: 0.7 ± 0.1, followup: 0.7 ± 0.1; passive rTMS pre-: 0.6 ± 0.0, post-assessment: 0.8 ± 0.1, followup: 0.7 ± 0.1) as shown in Figure 4.2. A time by treatment interaction existed for SICI ($F_{(2,542)}$ = 3.096, p = 0.46).

Behavioral Measures

No baseline between-group difference existed for grip strength (t = 0.25, p = 0.98). Grip strength in the paretic hand assessed pre-, post-, and 1-month post intervention remained unaltered as a main effect of time ($F_{(2,38)}$ = 0.432, p = 0.65) by functional rTMS (pre-: 7.22 ± 2.61, post-assessment: 6.88 ± 2.63, followup: 6.68 ± 2.38 N, respectively) or passive rTMS (pre-: 7.32 ± 3.13, post-assessment: 6.76 ± 3.09, followup: 7.07 ± 2.46 N). No time by treatment interaction existed for grip strength relationship ($F_{(2,38)}$ = 0.118, p = 0.89).

No baseline between-group difference existed for BBT (t = 0.630, p = 0.54). The number of blocks moved during the BBT improved as a main effect of time ($F_{(2,38)}$ = 4.380, p = 0.02) in the functional rTMS group (pre-: 21 ± 5, post-treatment: 25 ± 5, followup: 26 ± 6 blocks) and in the passive rTMS group (pre-: 18 ± 2, post-treatment: 19 ± 2, followup: 24 ± 5 blocks), while no difference existed between groups (F(2,38) = 0.320, p = 0.73) as depicted in Figure 4.3. Post hoc tests indicate that the only significant main effect of time occurred between pre-and post-treatment (t = 3.812, p < 0.01). No time by treatment interaction existed for BBT ($F_{(2,38)}$ = 0.320, p = 0.73).

No baseline between-group difference existed for the Fugl-Meyer Assessment (t = 0.993, p = 0.37). The Fugl-Meyer Assessment sum scores were not altered as an effect of time ($F_{(2, 38)}$ = 1.129, p = 0.33) secondary to functional rTMS (pre-: 60.36 ± 2.74, post-treatment: 63.27 ± 1.97, followup: 60.55 ± 3.02) or passive rTMS (pre-: 56.60 ± 3.06, post-treatment: 56.50 ± 2.58, followup: 57.60 ± 2.35). No time by treatment interaction existed for the Fugl-Meyer Assessment ($F_{(2,38)}$ = 1.793, p = 0.18).

For the number of activities performed, no between-group differences existed at pre- (Z = 1.481, p = 0.14), post-assessment (Z = 1.517, p = 0.13) or followup (Z = 1.730, p = 0.09). For functional rTMS, a main effect of time existed for the number of activities performed ($\chi^2_{(2)}$ = 11.556, p < 0.01) (pre-: 19.6 ± 2.3, post-treatment: 18.7 ± 2.5, followup: 22.6 ± 2.0). *Post hoc* tests revealed no significant increase from pre- to post-treatment (Z = 0.832, p = 0.41), but a significant increase from pre-treatment to followup (Z = 2.554, p = 0.01), and a significant change from post-treatment to followup (Z = 2.668, p = 0.01). For passive rTMS, the number of activities performed was not affected by time ($\chi^2_{(2)}$ = 3.622, p = 0.16) (pre: 14.7 ± 2.8, post-treatment: 13.5 ± 2.2, , followup: 16.8 ± 2.3).

For the rating of how well activities were performed (Figure 4.4), no between-group differences existed at pre- (Z = 0.704, p = 0.52), post-assessment (Z = 0.951, p = 0.35) or followup (Z = 0.324, p = 0.35). For functional rTMS, a main effect of time existed for the how well activities were performed ($\chi^2_{(2)}$ = 11.128, p < 0.01) (pre-: 2.3 ± 0.5, post-treatment: 3.0 ± 0.4, followup: 3.2 ± 0.3). *Post hoc* tests revealed a significant increase from pre- to post-treatment (Z = 2.668, p < 0.01), no significant increase from post-treatment to followup (Z = 0.153, p = 0.88), and a significant change from pre-

treatment to followup (Z = 2.497, p = 0.01). For passive rTMS, the number of activities performed was not affected by time ($\chi^2_{(2)}$ = 0.462, p = 0.79) (pre-: 2.5 ± 0.2, post-treatment: 2.7 ± 0.2, followup: 2.8 ± 0.2).

Discussion

The present investigation aimed to compare alterations in cortical excitability subsequent to eight sessions of functional rTMS or passive rTMS intervention in survivors of stroke. As hypothesized, functional rTMS increased cortical excitability to a greater degree than passive rTMS. SICI remained unaltered in both groups. Due to this finding, a strong likelihood exists that both intervention paradigms primarily influenced excitatory interneurons at the motor cortex. A second objective was to compare alterations in behavioral assessment scores in the intervention schemes outlined above. We hypothesized that functional rTMS would enhance behavioral outcomes to a greater degree than passive rTMS as assessed by the greater increases in both Fugl-Meyer, BBT, grip strength, and the MAL scores. Although both groups' behavioral scores improved in some metrics, neither intervention proved superior.

Our finding of functional rTMS enhancement of ICF across multiple sessions, extends Massie et al.'s finding that a single treatment session of functional rTMS enhanced ICF to a greater degree than passive rTMS.[219] After a single functional rTMS treatment, SICI was found to be enhanced by passive rTMS and was down-regulated following functional rTMS[219] Muscular force steadiness, used as a measure of behavioral ability by Massie et al. did not change in the functional rTMS group (in spite of increased intracortical excitability) while passive rTMS did enhance force

steadiness.[219] We found improvements in neuromuscular function to be similar between treatment types. This incongruence between studies could be subsequent to differences in treatment methodologies. A possibility exists that while a single dose of a given treatment may provide measurable improvement, the additive effect of multiples sessions of an alternate treatment may provide similar results. The resultant differences between the present and the previous study could also be secondary to the timing of assessments. While Massie et al. performed both intracortical and behavioral measures immediately post-treatment[219], the present study's assessments were performed approximately 24 hours post-treatment. The argument could be made that assessments made after acute treatment effects have washed out might be more representative of potential clinical efficacy in training as the conditioning effects of rTMS (as determined by ppTMS) vary by time elapsed between the cessation of conditioning and assessment.[220] Khedr et al., for example, found cortical alterations acutely induced by rTMS to be absent 2 hours post-conditioning.[221] Alternately, if training were to be introduced immediately post-treatment, these acute results could be advantageous. As functional rTMS does require some, albeit minor, degree of effort on the part of the participants it is possible that neural and/or muscular fatigue might influence both intracortical[222] and behavioral[223] results if made immediately post-treatment[224] as opposed to 24 hours post-treatment. The expectation would be that the effects of both rTMS and fatigue on cortical excitability would be present immediately post-treatment, but absent 24 hours post treatment.

The lack of behavioral differences between functional rTMS and passive rTMS are similar to studies comparing cyclical electrical stimulation of the upper extremity to

sEMG triggered electrical stimulation of the same musculature.[225] In this, both modes of treatment resulted in improved behavioral scores in a variety of assessment (e.g. BBT), but no time by treatment interaction was observed.[225]

For the purposes of this study, high frequency rTMS was applied to the lesion-affected motor cortex. If an alternate paradigm (e.g. low frequency rTMS applied to the non-lesion-affected motor cortex) was used the resultant alterations in cortical excitability and motor function may have been different. Several studies have found positive effects, both in terms of lesion-affected cortical excitability and behavioral ability[171,173,213,226,227] in survivors of stroke subsequent to receiving this mode of treatment. Inhibitory action of low frequency rTMS reduces the excitability of the non-lesion-affected motor cortex thereby simultaneously decreasing transcallosal inhibitory outflow to the lesion-affected motor cortex. The possibility exists that decreasing inhibition in such a way could be equal to if not more powerful than the facilitative action of high frequency rTMS. In a protocol similar to that used in the present study, EMG triggering of rTMS could result in inhibition of the non-lesion-affected hemisphere thereby allowing for decreased inhibition of the lesion-affected motor cortex.

Treatment increased ICF while SICI remained unaltered in both functional and passive rTMS. The ICF increase in functional rTMS proved to be greater than that of passive rTMS. This makes sense in that while both motor training[228] and rTMS[192] have been shown to increase ICF, the combination of the two may be synergistic. The lack of SICI decrease is somewhat surprising in that a decrease in GABAergic signaling is associated with motor training.[229] On the other hand, a recent investigation into the effect of rTMS on SICI found no difference in SICI amplitude.[230] This leads to the notion

that the effects of functional rTMS, in terms of SICI, are more similar to rTMS interventions than that of motor training.

Conclusion

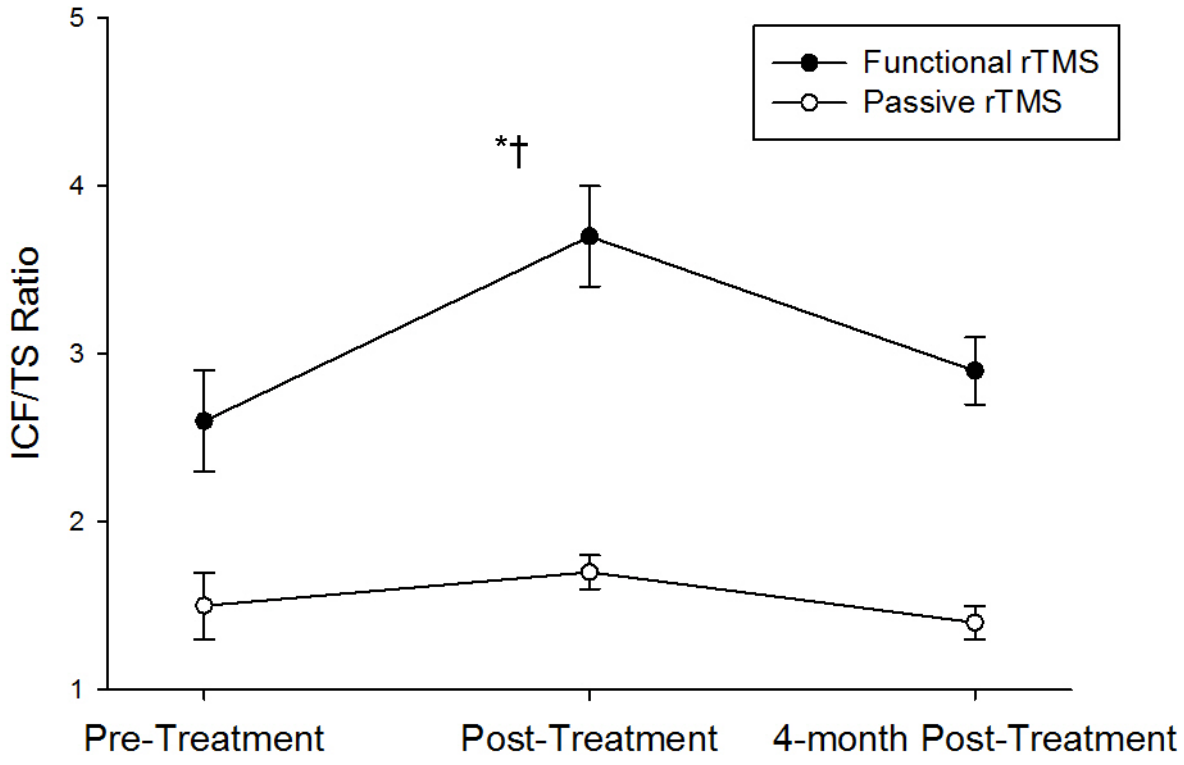
Functional rTMS provided a greater degree of neurophysiological effect, but little benefit in behavioral measures as compared to passive rTMS. Both groups, however, demonstrated some level of enhanced function as an effect of time. This finding addresses a lack of information upon comparison of functional rTMS to traditional research models of rTMS intervention in survivors of stroke. The present study supports the use of rTMS as a rehabilitation treatment post-stroke as both cortical excitability and behavioral measures were improved subsequent to both functional and passive rTMS interventions.

Tables

Table 4.1. Subject Demographics.

Participant	Group	Sex	Age (years)	Stroke to Treatment (months)	CVA Hemisphere	Stroke Location
1	passive	male	44	8	right	cortical + subcortical
2	functional	female	42	36	left	cortical + subcortical
3	passive	female	74	60	right	subcortical
4	passive	female	66	82	left	subcortical
5	passive	female	61	16	other	other
6	passive	male	74	48	other	brainstem
7	passive	male	86	49	other	other
8	passive	male	63	166	left	cortical + subcortical
9	functional	male	68	19	left	cortical + subcortical
10	functional	male	54	9	left	basal ganglia
11	passive	female	65	21	left	cerebellum
12	functional	female	75	37	right	subcortical
13	functional	female	41	6	right	cortical + subcortical
14	functional	male	51	72	left	cortical + subcortical
15	functional	female	63	36	right	subcortical
16	functional	male	70	56	left	cortical + subcortical
17	functional	female	64	44	left	subcortical
18	functional	male	70	32	right	subcortical
19	passive	male	77	23	right	brain stem
20	passive	male	63	15	left	subcortical
21	functional	female	21	145	left	subcortical

Figures



*Greater than Pre-Treatment in both groups (p<0.05)
†Functional greater than passive rTMS (p<0.05)

Figure 4.1. Intracortical Facilitation (ICF). ICF (MEP_{15ms} / $MEP_{TS(avg)}$) was enhanced in both groups, but to a greater degree in functional rTMS. This ICF ratio for each individual ICF trial to the average TS value in each subject's assessment session was established to identify the degree of facilitation present, while controlling for inter-assessment baseline excitability variability.

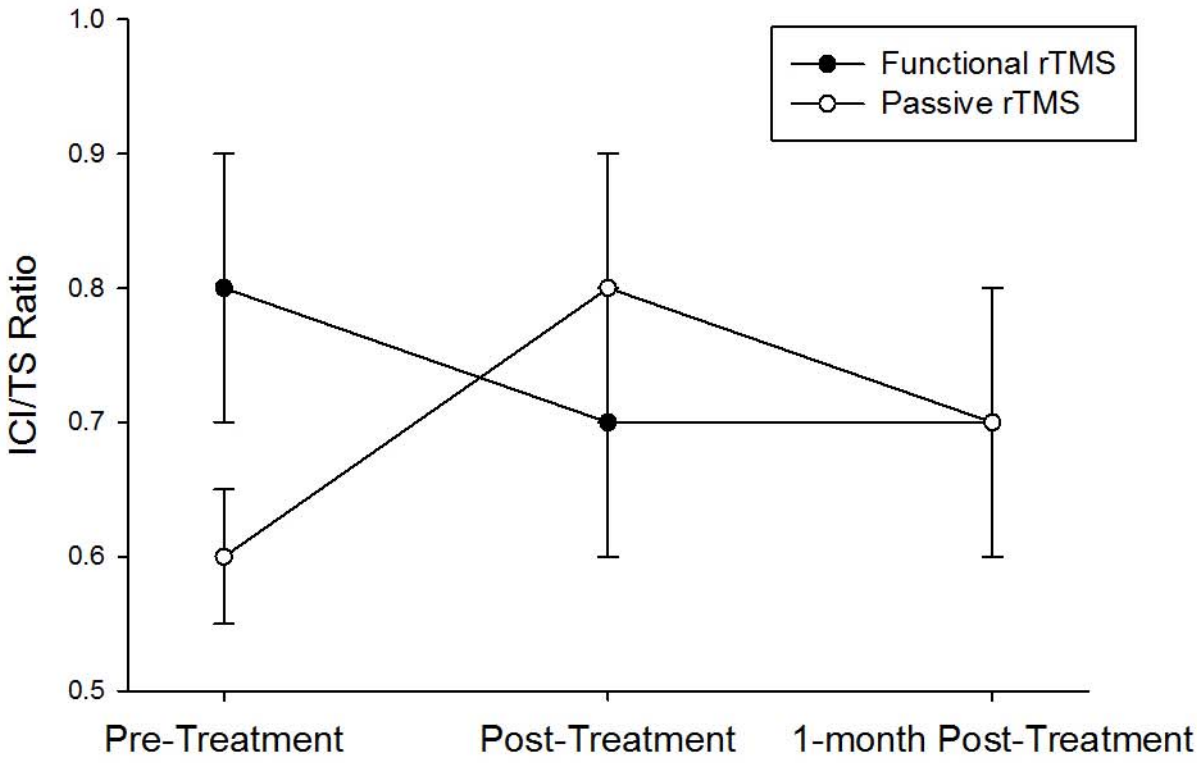
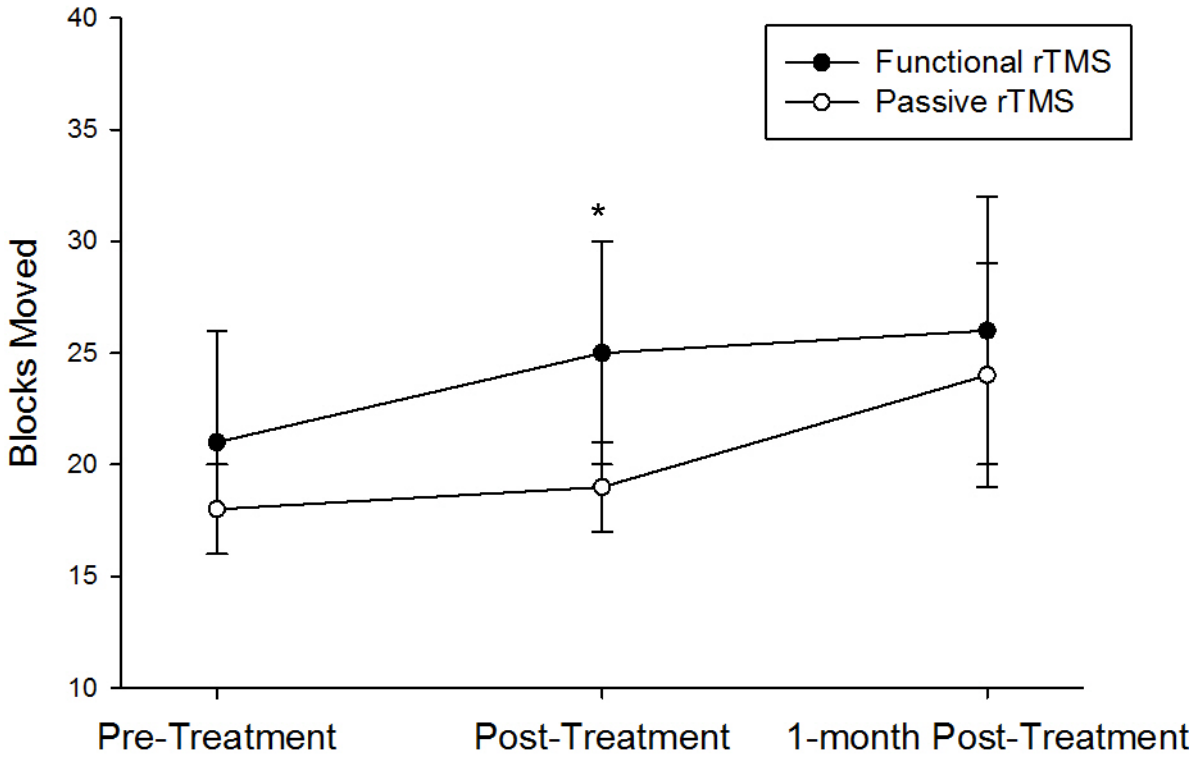
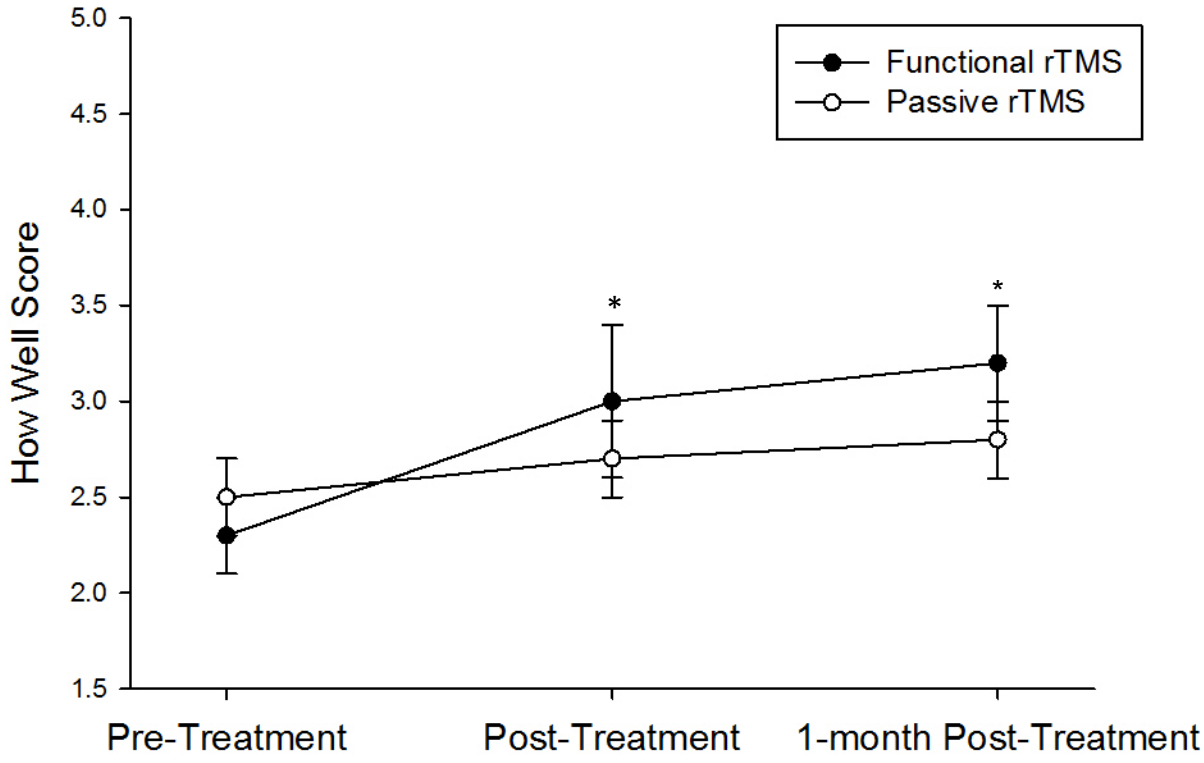


Figure 4.2. Short-term Intracortical Inhibition (SICI). SICI (MEP_{2ms} / $MEP_{TS(avg)}$) was unaffected by either intervention. This SICI ratio for each individual SICI trial to the average TS value in each subject's assessment session was established to identify the degree of facilitation present, while controlling for inter-assessment baseline excitability variability.



*Greater than Pre-Treatment in both groups (p<0.05) increase in the number of blocks moved.

Figure 4.3. Box and Block Test. Both functional rTMS and passive rTMS facilitated an increase in the number of blocks moved.



*Greater than Pre-Treatment in functional rTMS (p<0.05)

Figure 4.4. Motor Activity Log. Functional rTMS allowed for enhancement of how well participants judged their motion to be.

CHAPTER VI – OVERALL CONCLUSIONS

Neuromuscular dysfunction can arise in the central nervous system or the peripheral nervous system. These conditions range from natural progressions, such as aging, to acute insults, such as stroke. The overall objective of the four projects discussed herein was the enhanced characterization and treatment of several modes of neural dysfunction: stroke, peripheral neuropathy, and healthy aging.

The contribution of neuromuscular control of ankle force to postural stability was investigated in both healthy aging and peripheral neuropathy. Both advanced age and peripheral neuropathy involved a greater correlation of ankle force control to postural stability. This suggests a greater reliance on the ankle strategy in these conditions. This suggests that training regimens for enhanced ankle control could pay off in terms of postural stability.

Repetitive transcranial magnetic stimulation was used as a treatment intervention in survivors of stroke. The goal of this scheme was to enhance neuroplasticity. Cortical outcomes suggest that the central nervous system was impacted by these treatments. Translation to functional outcomes, however, was elusive. This suggests that repetitive transcranial magnetic stimulation has the potential to provide benefit to survivors of stroke, but that finding the optimal treatment scheme is of key importance.

Though the conditions investigated over the course of these four studies are diverse, the common theme of neural lesions manifesting as functional deficit is present through all of them. The findings of these four studies improved the characterization of

stroke, aging, and peripheral neuropathy. More importantly, these findings are likely to contribute to future treatments and rehabilitation techniques with the goal of improved neuromuscular function thereby improving quality of life.

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APPENDIX

Informed Consent for Manuscript #1

Consent to Participate in a Research Study

Colorado State University

TITLE OF STUDY: *Ankle Steadiness, Postural Control, and Physical Frailty*

PRINCIPAL INVESTIGATOR: *Brian L. Tracy, Ph.D. 491-2640*

CO-INVESTIGATOR: *Raoul Reiser II, Ph.D. 491-6958*

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH? *You are a man or woman between the ages of 18-30 or 65-95 years. You either 1) do not report major health problems, or 2) report problems with falling and/or frailty. Our research is looking at the effect of healthy and frail aging, and contributions to the control of muscle force.*

WHO IS DOING THE STUDY? *This research is being performed by Brian Tracy, Ph.D., and Raoul Reiser II, PhD of the Health and Exercise Science Department. Trained graduate students, undergraduate students, research associates, or research assistants are assisting with the research. These studies are paid for by the National Institutes of Health, a part of the US Government.*

WHAT IS THE PURPOSE OF THIS STUDY? *The way in which muscles are controlled by the brain and nerves may change in older people. The effect of vision, mental distraction, and/or vibratory stimuli feedback may be different in young, healthy elderly, and frail elderly, and may be different between muscles. The purpose of the research is to examine these changes and differences in hand, arm, and leg muscles.*

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST? *This whole research project will take place over a period of approximately two years. Your part in this study will take place over five to seven visits over a period of eight weeks.*

WHAT WILL I BE ASKED TO DO? *This consent form applies to a large research project. You are only being asked to participate in parts of the total project. Depending on the part of the research project that you are involved in, you will be asked to participate in some of the following procedures. Many potential procedures are described in the section below. However, the procedures that you will be asked to do for this part of the study have a check mark next to them. The check marks were put there*

by one of the researchers. A member of the research team will fully explain each checked procedure that applies to your participation.

_____ *You will be asked to answer some questions about your health and exercise to determine if you can participate in the study. (~ 30 minutes)* _____ *(your initials)*

_____ *If you are in the 65-95 yr-old age group, you will be asked to undergo a brief physical exam by a physician. This test will occur in the Human Performance Clinical/Research Laboratory in the Department of Health and Exercise on the CSU campus. (~ 15 minutes)* _____ *(your initials)*

_____ *The fat, muscle, and bone in your body will be measured using an x-ray device (dual-energy x ray absorptiometer) that will scan you from head to toe while you lie quietly on a special table for approximately 10 minutes. The amount of x-ray radiation you will receive is extremely low.* _____ *(your initials)*

_____ *You will be asked to lightly warm-up your arms and legs with light stretching, simple footwork and slow walking at a comfortable level. (~ 5 minutes)*
_____ *(your initials)*

_____ *You will be asked to complete brief mental tests of your ability to remember words and numbers on two separate occasions. (~ 20 minutes)*
_____ *(your initials)*

_____ *You will perform a short physical performance test comprised of simple one-legged and two-legged balance tests with your eyes open or closed, rising from a chair five times, and walking a short distance. (~ 20 minutes)*
_____ *(your initials)*

_____ You will be asked to ascend and descend a staircase at a pace comfortable to you. A handrail and research assistant will be within close reach at all times for

assistance. (~ 2 minutes)

_____ *(your initials)*

_____ You will undergo clinical examination of the sensory capacity using fine filaments and probes on the skin surface to measure sensory capacity._____ (your initials)

_____ *While standing, you will complete two different stepping tests. You will be asked to step as rapidly as possible to the front, side, and rear. (~20 minutes)*

_____ *(your initials)*

_____ *You will perform three reaction time tests with a computer and keyboard. You will respond to either a symbol on the computer screen or a brief sound.(~15 minutes)*

_____ *(your initials)*

_____ *You will perform a mobility test. This will involve rising from a chair, walking 10 feet, turning around, walking back to the chair, and sitting down. This will be repeated three times. (~5 minutes)*

_____ *(your initials)*

_____ *You will stand next to a wall and reach your arm out as far as you can without moving your feet. This task will be attempted and measured three times. (~2 minutes)*

_____ *(your initials)*

_____ *You will sit in a special chair and perform light and heavy muscle contractions with your hand, arm, thigh and/or ankle muscles while your leg, hips, and shoulders are comfortably secured. (1 – 2.5 hours)*

_____ *(your initials)*

_____ *You will stand as still as possible for 15-60 seconds with your feet together and arms by your side. This will be performed several times in a row with several minutes rest between each trial. During some of the trials you will look forward at a point on a wall in front of you. During some of the trials you will have your eyes closed. During this*

test you will be standing on a device called a force plate that measures the forces that your feet apply on the surface. (~20 minutes) _____ *(your initials)*

_____ *You will stand on the force plates and gently sway or lean forwards and backwards without falling while keeping your feet flat for 60-90 seconds. You will be spotted by a research assistant. (~20 minutes)* _____ *(your initials)*

_____ *You will stand in place while keeping your feet flat for approximately a minute on the force plates while a small weight disrupts your stance gently. (~20 minutes)*
_____ *(your initials)*

_____ *While performing light and heavy muscle contractions or standing tasks, you may be asked to perform a slightly challenging counting drill out loud during the task. (1-2.5 hours)*

_____ *(your initials)*

_____ *Sticky electrodes will be placed on the skin over the muscles involved for some of the visits and will remain in place until the end of that visit. Natural oil in the skin will be removed with rubbing alcohol, and the skin will be gently roughened with a fine abrasive paste or cloth.* _____ *(your initials)*

_____ *An electrode made of hair-sized fine wires will be inserted into your hand, arm, thigh and/or ankle muscle using a small needle. The skin will be thoroughly disinfected, similar to when you get your blood drawn. The needle is sterilized and is the same as the ones used for blood drawing. Either the fine hair size wires or the needle will remain in your muscle for the duration of the visit and then will be removed. Usually there will only be one electrode insertion. However, it is possible that electrodes may need to be inserted 1-5 times in different locations in the muscle. (1-2.5 hours)*
_____ *(your initials)*

_____ *A vibrating device will be placed against leg muscle/tendon for a time period of several seconds up to several minutes, causing a brief muscle contraction.*
_____ *(your initials)*

_____ *An electrical stimulus will be delivered to a nerve or muscle in your leg or arm using a standard stimulator. This may cause a brief muscle contraction.*

_____ *(your initials)*

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY? *If you are not 18-30 or 65-95 years of age, are pregnant, are a regular smoker, or have any diseases that would affect our measurements, we will not be able to include you in the research.*

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS? *(The procedures that apply to your proposed participation are checked)*

_____ *Health questionnaires – There are no known risks associated with answering health questions. All information is kept strictly confidential.* _____ *(your initials)*

_____ *Physical examination – There are no known risks associated with a physician-administered physical examination.* _____ *(your initials)*

_____ *Warm-up – There are no known risks associated with completing this preventative task. It will be completed at a level comfortable to the subject.*

_____ *(your initials)*

_____ *Stair climb task – There is a slight risk of falling on the stairs during this test. There will be a research investigator near you for assistance and a handrail within reach at all times. Rest will be given to prevent tiredness.* _____ *(your initials)*

_____ *Brief mental Tests – There are no known risks associated with completing these tests. The information is confidential.* _____ *(your initials)*

_____ *Short physical performance test – There is a slight risk of falling and potential muscle strain during these tests. A research investigator will be spotting nearby at all times to prevent falls and rest will be given to prevent tiredness.*

_____ *(your initials)*

_____ *Sensory acuity exam – There is no risk associated with this task.*

_____ *(your initials)*

_____ *Rapid stepping test – There is a slight risk of soreness or muscle strain with these procedures. A researcher will be nearby for safety. Rest will be given to prevent tiredness.* _____ *(your initials)*

_____ *Reaction time – There are no known risks associated with the computer reaction time tests.* _____ *(your initials)*

_____ *Mobility test – There is a slight risk of falling and injury as a result of rising from a chair and walking a short distance. A research investigator will be nearby to help. Rest will be given to prevent tiredness.* _____ *(your initials)*

_____ *Standing reach test – There is a slight risk of falling or muscle strain from this test. You will be next to a wall to help keep balance. A research investigator will be next to you for safety.* _____ *(your initials)*

_____ *Muscle contractions – There is a slight risk of muscle strain and muscle soreness resulting from brief, light and strong muscle contractions with the hand, arm, thigh and/or ankle. Soreness should not last more than two days or affect your normal function.* _____ *(your initials)*

_____ *Postural Standing – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and be closely surrounded by a padded handrail and a research assistant.* _____ *(your initials)*

_____ *Postural Sway – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and be closely surrounded by a padded handrail and a research assistant.* _____ *(your initials)*

_____ *Perturbed Standing – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and you will have a security rail, a research assistant near and a cord attached to the ceiling to prevent you from falling if you lose your balance.* _____ *(your initials)*

_____ *Counting drill - There is a minimal risk of feeling anxious while counting and performing muscle contractions or standing. Although, trials will be less than 30 seconds at a time and are not meant to be strenuous. The task will be terminated if you feel uncomfortable.* _____ *(your initials)*

_____ *Sticky electrodes – There is no known risk with the preparation or use of sticky electrodes on the surface of the skin.* _____ *(your initials)*

_____ *Fine-wire electrodes – There is a risk of discomfort from the needle, temporary soreness in that muscle, and a remote risk of infection. The equipment we use is sterile and only used once and then thrown away. We use special procedures to kill the germs on the skin. In cases where we keep the needle in the muscle during the test, it may cause slightly more discomfort.* _____ *(your initials)*

_____ *Vibration of muscle or tendon – There is no known risk associated with vibration of your tendon or muscle. The sensation you will feel is similar to what you would feel from a home massage device. The muscle that is vibrated may experience a small involuntary contraction.* _____ *(your initials)*

_____ *Electrical stimulus of nerve or muscle – There is no known risk associated with electrical stimulation of nerves or muscle. The device is isolated from dangerous electrical voltages. You will experience a mild sensation of electrical shock in your arm*

or leg when we stimulate with low levels. When we stimulate with higher levels, you will likely experience a brief but uncomfortable sensation of electrical shock. The electrical stimuli will likely cause an involuntary muscle contraction. _____ *(your initials)*

_____ *Body composition (DEXA) scan – the risks associated with the DEXA are very low. The radiation you will receive is less than 1/3000th of the Food and Drug Administration (FDA) limit for annual exposure. The FDA is a government organization responsible for medical safety. In other words, you could receive 3000 DEXA scans in a single year and still not meet the FDA limit for radiation exposure. In this study you will receive one scan. The more radiation you receive over the course of your life, the greater the risk of having cancerous tumors or of inducing changes in genes. The radiation in this study is not expected to greatly increase these risks, but the exact increase in such risks is not known. Women who are pregnant or could be pregnant should receive no unnecessary radiation and should not participate in this study.*
_____ *(your initials)*

It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY? *There are no direct benefits to you for participating in this study except the health information from the body composition assessment.*

DO I HAVE TO TAKE PART IN THE STUDY? *Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.*

WHAT WILL IT COST ME TO PARTICIPATE? *There is no cost to you for participating except that associated with your transportation to our facilities.*

WHO WILL SEE THE INFORMATION THAT I GIVE? *We will keep private all research records that identify you, to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court, the National Institutes of Health, or to the Human Research Committee at CSU.*

CAN MY TAKING PART IN THE STUDY END EARLY? *Your participation in the study could end in the rare event of muscle strain, if you become pregnant, or if you miss an excessive number of appointments.*

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY? For experiments that involve fine wire electrodes, you will be paid $8/hr.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH? *Please be aware that for this study the University has made special arrangements to provide initial medical coverage for any injuries that are directly related to your participation in this research project. The research project will provide for the coverage of reasonable expenses for emergency medical care related to the treatment of research-related injuries, if necessary.*

LIABILITY:

Because Colorado State University is a publicly-funded, state institution, it may have only limited legal responsibility for injuries incurred as a result of participation in this study under a Colorado law known as the Colorado Governmental Immunity Act (Colorado Revised Statutes, Section 24-10-101, et seq.). In addition, under Colorado law, you must file any claims against the University within 180 days after the date of the

injury. In light of these laws, you are encouraged to evaluate your own health and disability insurance to determine whether you are covered for any physical injuries or emotional distresses you might sustain by participating in this research, since it may be necessary for you to rely on your individual coverage for any such injuries. Some health care coverages will not cover research-related expenses. If you sustain injuries, which you believe was caused by Colorado State University or its employees, we advise you to consult an attorney. Questions concerning treatment of subjects' rights may be directed to Janell Barker, Human Research Administrator at 970-491-1655.

WHAT IF I HAVE QUESTIONS? *Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Brian Tracy, Ph.D., at (970)491-2640, or via email at tracybl@cahs.colostate.edu. If you would like to ask a medical doctor about your participation in the study, you may contact Russell Risma, M.D. at (970) 491-7121, or page Wyatt Voyles M.D. at (970) 202-4020. If you have any questions about your rights as a volunteer in this research, contact Janell Barker, Human Research Administrator at (970) 491-1655. We will give you a copy of this consent form to take with you.* Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 6 pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____

Printed name of person agreeing to take part in the study

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff

Informed Consent for Manuscript #2

Consent to Participate in a Research Study

Colorado State University

TITLE OF STUDY: *Postural steadiness and ankle control in diabetic neuropathy*

PRINCIPAL INVESTIGATOR: *Brian L. Tracy, Ph.D. 491-2640*

CO-PRINCIPAL INVESTIGATOR: *Raoul F. Reiser II, Ph.D., C.S.C.S.*

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH? *You are a man or woman between the ages of 65-90 years, you have diabetic neuropathy in both feet, and you do not report having other neurologic disorders. Our research is looking at the impact of diabetic neuropathy on ankle muscle force control and postural steadiness.*

WHO IS DOING THE STUDY? *This research is being performed by Brian Tracy, Ph.D. and Raoul Reiser, Ph.D. of the Health and Exercise Science Department. Trained graduate students, research associates, research assistants or undergraduate students assist with the research. This study is funded by the Center on Aging, Colorado State University.*

WHAT IS THE PURPOSE OF THIS STUDY? *To examine the effect of diabetic neuropathy on the control of ankle muscle force and the control of standing posture. This study, more specifically, will determine the contribution of degraded ankle sensation to ankle control and postural steadiness.*

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST? *This whole research project will take place over a period of approximately one year.*

However, your part of this study will be two to three visits over a period of several days.

_____ *(your initials)*

WHAT WILL I BE ASKED TO DO? *You will be asked to participate in the following procedures. Many potential procedures are described in the section below. However, the procedures that you will be asked to do <u>for this study</u> have a check mark next to them. The check marks were put there by one of the researchers. A member of the research team will fully explain each checked procedure that applies to your participation.*

_____ *You will be asked to answer some questions about your health and exercise to determine if you can participate in the study. (~ 30 minutes)*

_____ *(your initials)*

_____ *You will be asked to undergo a brief exam by a physician. This test will occur in the Human Performance Clinical/Research Laboratory in the Department of Health and Exercise on the CSU campus. (~ 15 minutes)*

_____ *(your initials)*

_____ *You will undergo clinical examination of the sensory degeneration in the lower limb. This will determine the extent of the neuropathy. Fine filaments and probes will be used to measure sensory capacity.*

_____ *(your initials)*

_____ *The fat, muscle, and bone in your body will be measured using an x-ray device (dual-energy x ray absorptiometer) that will scan you from head to toe while you lie quietly on a special table approximately for 10 minutes. The amount of x-ray radiation you will receive is extremely low.*

_____ *(your initials)*

_____ *You will be asked to lightly warm-up your legs with light stretching, simple footwork and slow walking. (~ 10 minutes)*

_____ *(your initials)*

_____You will sit or lie down in a special chair and perform light and heavy muscle contractions with your ankle muscles while your hips and shoulders are comfortably secured. (1 – 2.5 hours) *_____ (your initials)*

_____ Sticky electrodes will be placed on the skin over the muscles involved and will remain in place until the end of the visit. Natural oil in the skin will be removed with rubbing alcohol, and the skin will be gently roughened with a fine abrasive paste or cloth. *_____ (your initials)*

_____ An electrode made of hair-sized wires will be inserted into your leg muscle using a small needle. The skin will be thoroughly disinfected, similar to when you get your blood drawn. The needle is sterilized and is the same as the ones used for blood drawing. Either the hair-sized wires or the needle will remain in your muscle for the duration of the visit and then will be removed. Usually there will only be one electrode insertion. However, it is possible that electrodes may need to be inserted 1-5 times in different locations in the muscle. *_____ (your initials)*

_____ A vibrating device, the size of a large coin, will be placed on the front and/or back of your ankle giving a subtle vibration for a time period of 10-60 seconds, causing a brief muscle contraction. This sensation will be painless.

_____ (your initials)

_____ You will stand as still as possible for 15-60 seconds with your feet together and arms by your side. This will be performed several times in a row with several minutes rest between each trial. During some of the trials you will look forward at a point on a wall in front of you. During some of the trials you will have your eyes closed. During this test you will be standing on a device called a force plate that measures the forces that your feet apply on the surface. There will be a security rail surrounding you to prevent falling and a research assistant spotting you.

_____ (your initials)

_____ *You will stand on the force plates and gently lean forwards and backwards without falling while keeping your feet flat for 60-90 seconds. You will be spotted by a research assistant.* _____ *(your initials)*

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY? *If you are not 65-90 years of age, are pregnant, are a regular smoker, or have any diseases that would affect our measurements, we will not be able to include you in the research.*

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS? *(The procedures that apply to your proposed participation are checked)*

_____ *Health questionnaires – There are no known risks associated with answering health questions. All information is kept strictly confidential.*

_____ *(your initials)*

_____ *Clinical/Physical examination – There are no known risks associated with a physician-administered physical examination.*

_____ *(your initials)*

_____ *Muscle contractions – There is a slight risk of muscle strain and muscle soreness resulting from brief strong muscle contractions. Soreness should not last more than two days or affect your normal function.*

_____ *(your initial)*

_____ *Fine-wire electrodes – There is a risk of discomfort from the needle, temporary soreness in that muscle, and a remote risk of infection. The equipment we use is sterile and only used once and then thrown away. We use special procedures to kill the germs on the skin.* _____ *(your initials)*

_____ *Vibration of muscle or tendon – There is no known risk associated with vibration of your tendon or muscle. The sensation you will feel is similar to what you would feel from a home massage device. The muscle that is vibrated may experience a small, harmless involuntary contraction.* _____ *(your initials)*

_____ *Body composition (DEXA) scan – the risks associated with the DEXA are very low. The radiation you will receive is less than 1/3000th of the Food and Drug Administration (FDA) limit for annual exposure. The FDA is a government organization responsible for medical safety. In other words, you could receive 3000 DEXA scans in a single year and still not meet the FDA limit for radiation exposure. In this study you will receive one scan. The more radiation you receive over the course of your life, the greater the risk of having cancerous tumors or of inducing changes in genes. The radiation in this study is not expected to greatly increase these risks, but the exact increase in such risks is not known. Women who are pregnant or could be pregnant should receive no unnecessary radiation and should not participate in this study.*
_____ *(your initials)*

_____ *Postural Sway – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and be closely surrounded by a padded handrail and a research assistant.*

_____ *(your initials)*

_____ *Sensory Degradation Exam – There is no risk associated with this task.*
_____ *(your initials)*

_____ *Lower Limb Warm-Up – There is no known risk associated with this task.*
_____ *(your initials)*

_____ *<u>Sticky Electrodes</u> – There is no risk with using these electrodes.*

_____ *(your initials)*

It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY? *There are no direct benefits to you for participating in this study except the health information from the body composition assessment.*

DO I HAVE TO TAKE PART IN THE STUDY? *Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.*

WHAT WILL IT COST ME TO PARTICIPATE? *There is no cost to you for participating except that associated with your transportation to our facilities.*

WHO WILL SEE THE INFORMATION THAT I GIVE? *We will keep private all research records that identify you, to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court or to the Institutional Review Board at CSU.*

CAN MY TAKING PART IN THE STUDY END EARLY? *Your participation in the study could end in the rare event of muscle strain, if you become pregnant, or if you miss an excessive number of appointments.*

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH? *Please be aware that for this study the University has made special arrangements to provide initial medical coverage for any injuries that are directly related to your participation in this research project. The research project will provide for the coverage of reasonable expenses for emergency medical care related to the treatment of research-related injuries, if necessary.*

LIABILITY:

Because Colorado State University is a publicly-funded, state institution, it may have only limited legal responsibility for injuries incurred as a result of participation in this study under a Colorado law known as the Colorado Governmental Immunity Act (Colorado Revised Statutes, Section 24-10-101, et seq.). In addition, under Colorado law, you must file any claims against the University within 180 days after the date of the injury. In light of these laws, you are encouraged to evaluate your own health and disability insurance to determine whether you are covered for any physical injuries or emotional distresses you might sustain by participating in this research, since it may be necessary for you to rely on your individual coverage for any such injuries. Some health care coverages will not cover research-related expenses. If you sustain injuries, which you believe was caused by Colorado State University or its employees, we advise you to consult an attorney. Questions concerning treatment of subjects' rights may be directed to Janell Barker, Human Research Administrator at 970-491-1655.

WHAT IF I HAVE QUESTIONS? *Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Brian Tracy, Ph.D., at (970)491-2640, or via email at tracybl@cahs.colostate.edu. If you would like to ask a medical doctor about your participation in the study, you may contact Russell Risma, M.D. at 491-7121, or _____ at _____. If you have any questions about your rights as a volunteer in this research, contact Janell Barker, Human Research Administrator at 970-491-1655. We will give you a copy of this*

consent form to take with you. Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 5 pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____

Printed name of person agreeing to take part in the study

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff

Informed Consent for Manuscript #3

Consent to Participate in a Research Study

Colorado State University

TITLE OF STUDY: **rTMS as an adjunct to constraint-induced therapy: a randomized controlled trial**

PRINCIPAL INVESTIGATOR: Matt Malcolm, Ph.D.

Department of Occupational Therapy

Colorado State University

Fort Collins, CO 80524

(970) 491-6243

malcolm2@cahs.colostate.edu

CO-PRINCIPAL INVESTIGATOR: Gerald McIntosh, MD

Department of Music, Theatre, & Dance

Colorado State University

Fort Collins, CO 80524

(970) 482-4373

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH? You are an adult man or woman aged 40 years or older. You have had a stroke at least 9 months ago that has affected your ability to use your arm and hand. You are not pregnant. You do not have a heart pacemaker or other medical device in your body. You have never had a seizure.

WHO IS DOING THE STUDY? This study is part of a combined effort between Matt Malcolm, Ph.D. in the Department of Occupational Therapy at Colorado State University and Gerald McIntosh, MD a neurologist at Poudre Valley Hospital and associate of the Department of Music, Theatre, and Dance at Colorado State University. This study is funded by the National Center for Medical Rehabilitation Research, which is part of the National Institutes of Health.

WHAT IS THE PURPOSE OF THIS STUDY? The purpose of this research study is to determine if magnetic brain stimulation plus therapy improves recovery of movement more than therapy alone. The procedures described for this study are experimental. Approximately 30 individuals will be studied.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST? The study will take place mainly in the NeuroRehabilitation Research Laboratory (NRRL) at Colorado State University. Some initial screening/testing procedures will take place at Poudre Valley Hospital.

WHAT WILL I BE ASKED TO DO? We will meet with you to determine if you meet the initial study requirements and ask you to obtain approval from your primary care physician. We will provide you with an informational letter for your physician to sign indicating that he or she is providing medical clearance for you to participate. This letter will also provide contact information for our laboratory, should your physician have any questions. We will also include a copy of this form for your physicians records. If you do not meet initial requirements, you will not participate in the study. If you do meet these requirements, you will participate with two procedures to determine further eligibility. These procedures are: magnetic resonance imaging (MRI), and electroencephalogram (EEG). The purpose of the MRI is to confirm the type of stroke you had. If you have had a stroke that resulted from a hemorrhage (bleeding in the brain), you will not be allowed to participate in the study due to safety reasons. The purpose of the EEG is to determine if you may be prone to seizures. Seizures are brain disorders that can result from damage to the brain or atypical brain development.

Once the researchers have verified that you have not had a hemorrhagic stroke, you do not have signs of seizure activity, and that you meet all other study criteria, you will be asked to participate with the pre-treatment evaluation session. This session will last approximately 5 to 6 hours. This and all other evaluation sessions will allow the researchers to determine how much and how well you are able to use your stroke-affected arm, how stroke has affected your overall life, and to evaluate the activity level of your nervous system.

One to three days after the pre-treatment evaluation session, you will begin the therapy phase of the study, which will last for 2 weeks, excluding weekends. On each weekday

during this period, you will come to the NRRL for magnetic brain stimulation and therapy. Depending upon your group assignment you may receive real or artificial brain stimulation, which is randomly determined. You will not be told which type of stimulation you are receiving because knowing could affect your response to the treatments. Real magnetic stimulation uses changes in magnetic fields in the brain producing electrical currents, which may affect brain activity and function. Artificial stimulation does not produce these same effects on brain activity or function. Before real or artificial brain stimulation begins, we will first find your motor threshold. Motor threshold is the stimulation intensity that produces a muscle response during magnetic stimulation. We will use the motor threshold number to help determine the proper intensity (slightly below motor threshold) in which we will stimulate during real or artificial stimulation. Real or artificial brain stimulation will last for approximately 20 minutes, with additional time to set-up the equipment. During this stimulation you will be seated in a comfortable chair and asked to relax. We will connect electrodes (a type of sensor) to the skin over some your arm muscles. These electrodes stick to the skin, and will allow us to monitor muscle activity during stimulation. Once the brain stimulation period is complete, you will immediately begin movement therapy. During the movement therapy, you will practice moving your stroke-affected arm and hand to complete several different activities. Some example activities may include the following: washing a window, playing checker, picking up small objects, or preparing a snack. You will participate with movement therapy for approximately 5 hours each weekday during the therapy phase. Part of this therapy will include making and eating lunch.

During the 2-week therapy period, you will be asked to wear a padded safety mitt on the hand NOT affected by your stroke for 90% of the time you are awake each day. There are certain situations when you would not wear the mitt (for example in the shower, or when driving). A sample day might be something like the following: wake up, take a shower (remove mitt), eat breakfast (wearing mitt), drive to NRRL (remove mitt), participate in therapy at NRRL (wear mitt), drive home (remove mitt), eat dinner, read, brush teeth (wearing mitt), go to bed (remove mitt). The mitt is outfitted with a compliance device that measures the amount of time you wear the mitt each day. Even though you will not come for therapy on the weekends, you will still wear the mitt during on Saturday and Sunday as you do on weekdays. We will ask you to keep a home diary during the therapy period to provide us with details on your activities when not at NRRL.

Within a few days of your last therapy day, you will be asked to participate with the post-treatment evaluation. This session will allow us to measure changes in your abilities and nervous system that may have occurred during the therapy phase. We will also ask you to participate in a 4-month follow-up evaluation to determine any long-term changes.

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY?

You may be excluded from participating if any of the following are true:

You have had a hemorrhagic stroke

You have had or could have a seizure

You have a pacemaker or other implanted device or metal object in your upper body

You take medications that could increase your risk for having a seizure

You have had a brain injury leading to loss of consciousness

You have had or currently have a brain tumor

You have mental retardation, uncontrolled psychiatric or medical illness, or uncontrolled heart disease

You are pregnant

You are younger than 40 years of age

We will ask you to complete a basic health questionnaire to provide us with information regarding the above criteria.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks. The following sections describe risks associated with each primary aspect of the study:

<u>Screening MRI</u>.

You will be asked to participate with an MRI test to confirm the type of stroke you had. You will not have to pay for the MRI test, the study will pay for this cost. If you have had a stroke that resulted from a hemorrhage (bleeding in the brain), you will not be allowed to participate in the study due to safety reasons. Individuals who have a hemorrhagic stroke may be more prone to having a seizure during magnetic brain stimulation. Magnetic resonance imaging (MRI) is a procedure that allows doctors to look inside the

body by using a scanner that sends out a strong magnetic field and radio waves. This procedure is used routinely for medical care and is very safe for most people, but you will be monitored during the entire MRI scan in case any problems occur. The risks of MRI are:

- The MRI scanner contains a very strong magnet. Therefore, you may not be able to have the MRI if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. Someone will ask you questions about this before you have the MRI.

- There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system, and, in the event of an emergency, you can tell them to stop the scan. If have claustrophobia, you may require medication to help you relax ("sedation"). If you do require medication to relax, you should not drive a car, take part in activities like riding a bike, or perform other similar tasks until the next morning because the medication(s) can affect your thinking for several hours and can slow down your reflexes. If you do require a medication, you will need to obtain this from your own physician. None of the study staff will provide medications.

- The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of individuals. You will be given earplugs to reduce this risk.

- If you are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, if you are or may be pregnant, you should not participate with the MRI.

<u>Transcranial Magnetic Stimulation (TMS).</u>

TMS is considered a non-invasive technique to activate brain cells. There are, however, some risks associated with TMS. One primary risk factor the possibility of a seizure occurring. Guidelines to prevent seizures caused by TMS have been published and will be followed in conducting this study. TMS may cause a seizure in individuals that have a history of epilepsy or previous seizures. For this reason, any individual who has a history of epilepsy or seizures will be excluded from this study. TMS may also interfere with devices such as a heart pacemaker or deep brain stimulator. For this reason, individuals who have a pacemaker or other metal implants in the head, neck or upper body, will be excluded from this study. The Principal Investigator will ask you if you have a history of seizures or epilepsy, and if you have a pacemaker or other implanted metal device.

During the TMS procedure, you will feel a mild to moderate “tapping” on your scalp, which should not be painful. If this becomes uncomfortable for any reason, please alert the Principal Investigator or technician so that we may stop the procedure. For some people, TMS may cause a mild headache, which despite being uncomfortable, is harmless. These headaches typically occur due to local stimulation of the scalp and neck muscles. These headaches usually disappear shortly after the testing session, and may be responsive to mild analgesics (for example: Tylenol). If you develop a headache that is too uncomfortable during TMS, please notify the Principal Investigator so that the TMS procedure may be stopped.

Other risks that could occur with TMS include dental pain and mild hearing loss (we will have you where ear plugs to limit this risk). While repetitive TMS does not appear to have long-term negative effects, not all of the long-term effects are known. In the unlikely event that you have a seizure that is clearly caused by a study procedure, we will provide you with a letter, at your request, documenting this.

Constraint-Induced Therapy.

The movement therapy described above is called constraint-induced therapy. During part of this study, you will be wearing a mitt on the hand NOT AFFECTED by stroke. Using the mitt in an incorrect way might cause harm to you or others. We will, therefore, show you how to use the mitt correctly. You might feel tired sometimes throughout the therapy session. We have created rest breaks throughout the therapy so you do not feel so tired. You should tell the therapist if at anytime you are too tired to continue with treatment.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?

The benefits to you include: improved knowledge about your abilities, possibly improving your movement abilities, and increased awareness of how you use the arm that was affected by the stroke. Also, the information that comes out of this study may help improve the treatment of stroke in the future.

DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.

WHAT WILL IT COST ME TO PARTICIPATE? There are no direct costs associated with participating in this study.

WHO WILL SEE THE INFORMATION THAT I GIVE?

We will keep private all research records that identify you, to the extent allowed by law.

Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep you name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court. We will assign you a code number to maintain confidentiality (for example: CSU001).

Regulatory agencies, such as the Food and Drug Administration, may inspect records to ensure safety.

CAN MY TAKING PART IN THE STUDY END EARLY?

You may be withdrawn from the study *without* your consent for the following reasons:

You need a medical treatment not allowed in this study.

The investigator decides that continuing in the study would be harmful to you.

Study treatments have a bad effect on you.

You are not able to keep appointments.

You do not follow the instructions you are given, for example, you do not wear the mitt as instructed or fill out proper forms.

If the study sponsor decides to stop or cancel the study.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?

Upon completion of the pre-treatment evaluation, therapy phase, and post-treatment evaluation, you will receive a stipend in the amount of $100.00 to help offset some of the costs associated with your participation (for example, travel or lodging). This compensation with be spread out over four payments at the following times: $25 after pre-treatment evaluation, $25 after therapy phase, $25 after post-treatment, and $25 after follow-up testing (at 4 months post-treatment).

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH? The Colorado Governmental Immunity Act determines and may limit Colorado State University's legal responsibility if an injury happens because of this study. Claims against the University must be filed within 180 days of the injury.

WHAT IF I HAVE QUESTIONS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Matt Malcolm, PHD at (970) 491-6243. If you have any questions about your rights as a volunteer in this research, contact Janell Meldrem, Human Research Administrator at 970-491-1655. We will give you a copy of this consent form to take with you.

SIGNATURES

Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 5 pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____

Printed name of person agreeing to take part in the study

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff

Informed Consent for Manuscript #4

Consent to Participate in a Research Study

Colorado State University

TITLE OF STUDY: EMG-triggered functional motor cortex stimulation in stroke.

PRINCIPAL INVESTIGATOR: Matt Malcolm, Ph.D., OTR

Department of Occupational Therapy

Colorado State University

Fort Collins, CO 80524

(970) 491-2646

malcolm2@cahs.colostate.edu

CO-PRINCIPAL INVESTIGATOR: Crystal Massie, MS, OTR

Department of Occupational Therapy

Colorado State University

(970) 491-3444

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH? You are an adult man or woman aged 18 years or older. You have had a stroke at least 3 months ago that has affected your ability to use your arm and hand. You are not pregnant. You do not have a heart pacemaker or other medical device in your body. You have never had a seizure.

WHO IS DOING THE STUDY? This study is part of a combined effort between Matt Malcolm, Ph.D. and Crystal Massie, MS in the Department of Occupational Therapy at Colorado State University.

WHAT IS THE PURPOSE OF THIS STUDY? The purpose of this research study is to determine if using muscle activity to initiate magnetic brain stimulation impacts the nervous system and ability to control muscles differently than brain stimulation alone. The procedures described for this study are experimental. Approximately 30 individuals will be studied.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST? The study will take place mainly in the NeuroRehabilitation Research Laboratory (NRRL) in the Department of Occupational Therapy at Colorado State University. Some testing procedures will take place in the Physical Activity Laboratory in the Department of Health and Exercise Science at Colorado State University.

WHAT WILL I BE ASKED TO DO? We will meet with you to determine if you meet the initial study requirements. We will also ask you sign a medical release so that we may obtain a copy of your magnetic resonance imaging (MRI) or computerized tomography (CT) scans to establish the type or extent of your stroke. The purpose of the MRI or CT scan is to confirm the type and location of stroke you had. If you do not meet initial requirements, you will not participate in the study. If you do meet these requirements, you will participate with another procedure to determine further eligibility. This procedure is an electroencephalogram (EEG). The purpose of the EEG is to determine if you may be prone to seizures. Seizures occur because of abnormal activity in the brain. During the EEG, several recording electrodes (designed to record brainwave activity) will be applied to your scalp. You will then be asked to remain relaxed during the EEG recording. Following these screening procedures, we will provide you with a letter to give to your personal physician, along with a blank copy of this form, which will inform he or she about your participation in the study.

Once the researchers have verified that you meet all study criteria, you will be asked to participate with the initial evaluation. This and all other evaluation sessions will allow the researchers to determine how well you are able to use your stroke-affected arm and hand, and to evaluate the activity level of your nervous system. Testing will occur over two separate sessions (a morning and an afternoon testing session) each lasting approximately 2 to 3 hours. The following section describes the tests that will be done in the morning and afternoon initial testing sessions and what we will ask you to do during these tests. Once accepted into the study, you will need to come to the Colorado State University campus for a total of six days. The total number of hours involved in full participation in the study is approximately 20 hours.

Initial Evaluation Session (Pre-test)

MORNING SESSION

Location: Physical Activity Laboratory, Health and Exercise Science

Body composition measurement: We will measure your body composition to accurately determine the length and mass of body segments. We will use a Dual Energy Xray Absorptometry (DEXA) machine, which is like a large X-ray machine. During this procedure you will lay on the surface of the machine while a beam passes over your body. This procedure will last approximately 10 minutes.

Motion analysis: This test will use a motion capture system to precisely evaluate your arm and body movements during a reaching activity. We will apply light-weight reflective markers and surface electrodes on your torso and arms, and then have you perform a variety of movements with your stroke-affected arm. Motion capture systems will record the movement of your arm and muscle activity while you perform different reaching tasks.

Functional Movement Testing: We will ask you to participate with an evaluation of the functional movement of your stroke-affected arm. The evaluator will ask you to complete a series of movements (for example: lifting your arm out to the side, gripping a ball, and touching your nose). The evaluator will also time you move blocks from one bin to another—which will allows us to measure your ability to reach, grasp, transfer, and release objects using your stroke-affected hand and arm.

<BREAK/LUNCH>

AFTERNOON SESSION

Location: NeuroRehabilitation Research Laboratory, Occupational Therapy

Muscle Force Control: During this test, you will be asked to contract your stroke-affected forearm muscles against resistance. We will connect electrodes (a type of sensor) to the skin over some your arm muscles. These electrodes stick to the skin, and are designed to monitor muscle activity. We will ask you to perform light and strong contractions of the muscles that extend your wrist to measure your ability to control those muscles.

Transcranial Magnetic Stimulation testing: Using the same muscles and electrodes from the previous test, we will next assess the part of your nervous system that controls those muscles using transcranial magnetic stimulation (TMS). During the stimulation you will be seated in a comfortable chair. We will place a cloth cap on your head so that we are able to keep track of where we stimulate with the TMS. The magnetic

stimulation uses changes in magnetic fields in the brain producing electrical currents, which may affect brain activity and function. You will experience two different types of TMS in this testing. First, we will use single and paired pulses of TMS to measure the activity of your nervous system. Then we will use repetitive pulses of TMS, which will be a short and fast burst of TMS lasting 3 seconds. This will be followed by 30 seconds of rest, and then another short burst of fast TMS. This procedure will last approximately 20 minutes. We will then again use single and paired pulses to measure the activity of your nervous system.

Post-test and 1-month follow-up test

The same procedures and tests will be used for the post-test and 1 month-follow-up test as were used during the initial (pre) test, with two exceptions: 1) you will not receive repetitive TMS during these testing sessions, and 2) we will use single and paired pulse TMS once rather than twice during these testing sessions.

One to three days after the initial evaluation session, you will begin the brain stimulation phase of the study, which will last for 4 weekdays in a row. During the stimulation you will be seated in a comfortable chair. Depending upon your group assignment you may be asked to use your arm muscles while receiving the brain stimulation, which is randomly determined. The magnetic stimulation uses changes in magnetic fields in the brain producing electrical currents, which may affect brain activity and function. Before the brain stimulation begins, we will connect electrodes (a type of sensor) to the skin over some your arm muscles. These electrodes stick to the skin, and are designed to monitor muscle activity during stimulation. We will then determine your maximum muscle activity of forearm muscles that allow you to extend your wrist. You will be asked to bend your wrist back against some resistance while we record the amount of muscle activity. This will help determine the appropriate threshold for muscle activity. We will then find your motor threshold. Motor threshold is the magnetic stimulation intensity that produces a muscle response. We will use the motor threshold number to help determine the proper intensity (slightly below motor threshold) in which we will deliver the stimulation. The stimulation will last for approximately 30 minutes, with additional time to set-up the equipment. You will be asked to complete 2 sessions of brain stimulation each day with a rest period between the sessions.

Within 1 to 2 days of your last brain stimulation session, you will be asked to participate with the post-evaluation. This session will allow us to measure changes in your abilities and nervous system that may have occurred during the therapy phase. We will also ask you to participate in a 1-month follow-up evaluation to determine any long-term changes.

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY?

You may be excluded from participating if any of the following are true:

You have had or could have a seizure

You have a history of epilepsy

You have a pacemaker or other implanted device or metal object in your head or neck

You take medications that could increase your risk for having a seizure

You have had a brain injury leading to loss of consciousness within the last year

You have had or currently have a brain tumor

You have mental retardation, uncontrolled psychiatric or medical illness, or uncontrolled heart disease

You are pregnant

You are younger than 18 years of age

We will ask you to complete a basic health questionnaire to provide us with information regarding the above criteria.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks. The following sections describe risks associated with each primary aspect of the study:

<u>Electroencephalogram:</u>

The EEG recordings are performed according to standard practices within the field and are considered a non-invasive method to record brain activity. Risks associated with EEG include a possibility of skin tenderness around the area where the skin sensors are placed, but this is short lasting.

Transcranial Magnetic Stimulation (TMS):

TMS is considered a non-invasive technique to activate brain cells. There are, however, some risks associated with TMS. One primary risk factor is the possibility of a seizure occurring. Guidelines to prevent seizures caused by TMS have been published and will be followed in conducting this study. TMS may cause a seizure in individuals that have a history of epilepsy or previous seizures. For this reason, any individual who has a history of epilepsy or seizures will be excluded from this study. TMS may also interfere with devices such as a heart pacemaker or deep brain stimulator. For this reason, individuals who have a pacemaker or other metal implants in the head, neck or upper body, will be excluded from this study. The Investigator will ask you if you have a history of seizures or epilepsy, and if you have a pacemaker or other implanted metal device. Certain medications can increase the risk of a seizure occurring during TMS. For this reason, one section of the health questionnaire asks you to list medications you currently take and the dosage for each. This list will be reviewed by the study physician. If you are taking a medication that could increase the risk of having a seizure and you are unable to safely stop taking the medication, you will not be allowed to participate. **Importantly, if you stop taking any of these medications or you start taking a new medication or different dose of medication during your time in the study, you must immediately notify the researchers.** The study physician will review any such changes in your medications and you may have to stop participating in the study if the changes could increase your risk for having a seizure.

During the TMS procedure, you will feel a mild to moderate “tapping” on your scalp, which should not be painful. If this becomes uncomfortable for any reason, please alert the investigators or technician so that we may stop the procedure. For some people, TMS may cause a mild headache, which despite being uncomfortable, is harmless. These headaches typically occur due to local stimulation of the scalp and neck muscles. These headaches usually disappear shortly after the testing session, and may be responsive to mild analgesics (for example: Tylenol). If you develop a headache that is too uncomfortable during TMS, please notify the Investigator so that the TMS procedure may be stopped. Some individuals may experience inadvertent facial nerve stimulation during TMS and may experience facial twitching that may be uncomfortable for some. If you develop facial twitching that becomes uncomfortable during TMS, please notify the Investigator so that the TMS procedure may be stopped.

The investigators will take the following steps to monitor and manage the risk of a seizure during TMS.

1. Muscle responses will be monitored with electromyography (EMG) equipment during and after stimulation. EMG will allow the investigators to measure and monitor muscle responses during and after TMS. If the TMS causes a spread of excitability or

lasting excitation in your muscles, the investigators will see this on the EMG. If this occurs, TMS will be stopped.

2. If a seizure does occur, medical attention will be immediately requested by the investigators.

Other risks that could occur with TMS include dental pain and mild hearing loss. To limit the risk of hearing loss, we will apply earplugs to your ears, which we will ask you to wear during delivery of TMS. We will frequently re-check the earplugs to make sure they are staying in your ears. If you feel the earplugs become loose or fall out, please let us know immediately. We will stop TMS to correct the earplug placement. We will also stop TMS if we notice that the earplugs become loose.

While repetitive TMS does not appear to have long-term negative effects, not all of the long-term effects are known. In the unlikely event that you have a seizure that is clearly caused by a study procedure, we will provide you with a letter, at your request, documenting this.

Body Composition:

There is a small amount of radiation exposure associated with the DEXA, which is less than 1/20 of a typical chest x-ray. The more radiation one receives over the course of one's life, the more risk of having cancerous tumors or of inducing changes in genes. The changes in genes possibly could cause abnormalities or disease in a subject's offspring. The radiation in this study is not expected to greatly increase these risks, but the exact increase in such risks is unclear.

Instrumentation:

The devices used to measure biomechanics (i.e. arm movement) and muscle activity are non-invasive and pose no known risk.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?

The benefits to you include improved knowledge about your abilities and possibly improving your movement abilities. Also, the information that comes out of this study may help improve the treatment of stroke in the future.

DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.

WHAT WILL IT COST ME TO PARTICIPATE? There are no direct costs associated with participating in this study.

WHO WILL SEE THE INFORMATION THAT I GIVE?

We will keep private all research records that identify you, to the extent allowed by law.

Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep you name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court. We will assign you a code number to maintain confidentiality (for example: E01).

CAN MY TAKING PART IN THE STUDY END EARLY?

You may be withdrawn from the study *without* your consent for the following reasons:

You need a treatment not allowed in this study.

The investigator decides that continuing in the study would be harmful to you.

Study procedures have a bad effect on you.

You are not able to keep appointments.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?

You will be compensated a total of $75 for participating in the study; which will be separated into two payments. The total payment will be broken down as follows:

$50 paid following completion of the post-test.

$25 paid following completion of the 1-month follow up test.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH? The Colorado Governmental Immunity Act determines and may limit Colorado State University's legal responsibility if an injury happens because of this study. Claims against the University must be filed within 180 days of the injury.

WHAT IF I HAVE QUESTIONS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Matt Malcolm, PHD at (970) 491-2646. If you have any questions about your rights as a volunteer in this research, contact Janell Barker, IRB Senior Administrator at 970-491-1655. We will give you a copy of this consent form to take with you. This form has been approved by the CSU Institutional Review Board for the protection of human subjects as of July 15, 2011.

SIGNATURES

Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 5 pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____

Printed name of person agreeing to take part in the study

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff