Neuromuscular Determinants of Manual Dexterity and Walking Performance in Healthy Individuals and Persons with Multiple Sclerosis

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NEUROMUSCULAR DETERMINANTS OF MANUAL DEXTERITY AND WALKING PERFORMANCE IN HEALTHY INDIVIDUALS AND PERSONS WITH MULTIPLE SCLEROSIS

by

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

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Abstract

Almuklass, Awad Mohammed H (Ph.D., Integrative Physiology)

Neuromuscular Determinants of Manual Dexterity and Walking Performance in Healthy Individuals and Persons with Multiple Sclerosis

Thesis directed by Professor Roger M. Enoka

Motor control is the ability to produce and control movement, and is an outcome of various integrative mechanisms within the neurosensory, musculoskeletal, and neuromuscular systems. Impairment in motor function may originate from dysfunction of the central nervous system, the peripheral nervous system, or the muscular system. The NIH Toolbox for Assessment of Neurological and Behavioral Function includes tools to quantify motor function across the life span. There are four primary domains within the 'Toolbox': cognitive, motor, emotional, and sensory. The purposes of this dissertation were to investigate the neuromuscular and clinical determinants of manual dexterity and walking in healthy adults and individuals with multiple sclerosis; and to compare the effects of different types of electrical nerve stimulation on the walking performance of persons with multiple sclerosis.

The first study evaluated the capacity of an expanded set of force steadiness tasks to explain the variance in the time it takes young men and women to complete the grooved pegboard test. A stepwise, multiple-regression analysis indicated that much of the variance ($R^2 = 0.70$) in pegboard times could be explained by a model that comprised two predictor variables derived from the steadiness tasks: time to match the target during a rapid force-matching task and force steadiness (coefficient of variation for force) during a single-action task. Participants with slower pegboard times placed a greater emphasis on accuracy than speed as they had longer times to match the target during the rapid force-matching task and exhibited superior force steadiness during a force-matching task.

The second study compared the times to complete the four phases of peg manipulation and the forces applied to the pegboard during peg selection and insertion in persons with multiple sclerosis (MS) and three age groups of healthy adults. Multiple-regression models that could explain the variance in pegboard times for each group of participants were compared to assess the relative significance of the peg-manipulation attributes. Pegboard times for the MS group (104.2 ± 40.3 s) were longer than those for young (55.5 ± 6.7 s), middle-aged (57.5 ± 10.9 s), and old adults (80.6 ± 17.3 s). Regression analysis indicated that the pegboard times for the MS group could be predicted by the time for the peg-selection phase ($R^2 = 0.78$), whereas the predictors for young ($R^2 = 0.33$) and middle-aged ($R^2 = 0.78$) adults were the times for the peg-insertion and return phases, and the predictors for old adults ($R^2 = 0.49$) were the times for the peg-selection and
transport phases. The relative influence of peg-manipulation capabilities on a pegboard test of manual dexterity was greater for persons with MS and middle-aged adults than for young and old adults.

The third study examined the associations between neuromuscular characteristics of lower leg muscles and clinical assessments of physical function with walking performance of individuals who were moderately disabled by multiple sclerosis (MS). The regression models based on neuromuscular characteristics explained 40% of the variance in the 6-min walk distance and 47% of the variance in 25-ft walk time. The regression models that included the clinical assessments explained 63% of the variance in the 6-min walk distance and 47% of the variance in 25-ft walk time. Moderate amounts of the variance in two tests of walking performance were explained by the neuromuscular characteristics of lower leg muscles. The two walking tests were also significantly associated with a self-reported assessment of disability status and the time to complete the test of manual dexterity.

The fourth study compared the effects of a 6-wk intervention with either narrow- or wide-pulse NMES on walking performance of persons with relapsing-remitting MS. The NMES intervention was performed on the dorsiflexor and plantar flexor muscles of both legs at a tolerable level for 18 sessions across 6 wks. Outcomes were obtained before and after the intervention and 4 wks later. There was no influence of stimulus-pulse duration on the outcomes (P > 0.05), thus the data were collapsed across groups. A 6-wk intervention with NMES improved walking performance, strength of leg muscles, and fatigue in persons with relapsing-remitting MS. There was no influence of stimulus-pulse duration on the outcomes.

In summary, this dissertation examines the determinants of walking performance and manual dexterity in healthy adults and individuals with MS. The included studies show that neuromuscular electrical stimulation, regardless of current pulse and frequency, applied to lower leg muscles can improve walking performance in individual with MS.
DEDICATION

For their continuous love, support, and patience, this dissertation is dedicated to the most important five ladies in my life. My Mom Raida, my wife Saidah, and my three daughters: Mariam, Raida, and Jumanah.
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Dr. Enoka, special thanks to you for the support, help, and advice. I could not have done this work without your guidance and help. I am honored and proud to be one of your students. Forever, I will be your student doing the best work I can.

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CHAPTER I

REVIEW OF LITERATURE
INTRODUCTION

Motor control is the ability to produce and control movement, and is an outcome of various integrative mechanisms within the neurosensory, musculoskeletal, and neuromuscular systems. Impairment in motor function may originate from dysfunction of the central nervous system, the peripheral nervous system, or the muscular system. Critically, reductions in motor function lead to decreased mobility and increased risk of mortality (Katzmarzyk et al., 2002; Vestergaard et al., 2009). The NIH Toolbox for Assessment of Neurological and Behavioral Function (Gershon et al., 2010; Reuben et al., 2013) includes tools to quantify motor function across the life span (Reuben et al., 2013). There are four primary domains within the NIH Toolbox: cognitive, motor, emotional, and sensory. The motor domain assesses performance in locomotion, strength, endurance, balance, and dexterity. This review outlines the effects of aging and multiple sclerosis (MS) on motor function, the value of manual dexterity as an index of overall motor function, predictors of manual dexterity, and interventions to improve motor function in older adults and persons with MS.

MOTOR FUNCTION IN OLDER ADULTS

The decline in motor function experienced by healthy adults usually begins at age ~65 yrs (Hortobágyi et al., 2015). There are several underlying mechanisms. The nervous system starts to lose neurons and the surviving neurons have impaired function (Grounds, 2002; Mittal & Logmani, 1987; McNeil et al., 2005). With aging, axonal conduction speed is gradually reduced, which decreases reflex excitability
(Kido et al., 2004; Metter et al., 1998; Scaglioni et al., 2002). Motor unit architecture also changes with aging, as some denervated muscle fibers are reinnervated by the axons of surviving motor units, which increases single motor unit force (Galganski et al., 1993; Roos et al., 1997). In addition, muscle activation becomes more disorganized and less smooth compared with younger adults (Roos et al., 1997; Poston et al., 2013; Sleimen-Malkoun et al., 2013; Clark et al., 2014). These changes have functional consequences that impact daily life for older adults, such as reducing mobility and impairing manual dexterity.

**Mobility in Older Adults**

Relative to young adults, older adults experience decreases in muscle strength (Danneskiold-Samsoe et al., 2009), reductions in power (Dalton et al., 2010, 2014), loss of muscle mass (Cruz-Jentoft et al., 2010), impaired muscle activation (Clark et al., 2014), declines in balance (Papegaaij et al., 2014), coordination deficits (Brach & Vanswearingen, 2013), sensory dysfunction (Aagaard et al., 2010), mobility limitations (Beijersbergen et al., 2013), and cognitive impairment (Atkinson et al., 2007). The culmination of these adaptations results in movement becoming more difficult with advancing age. Specifically, older adults perform movements more slowly and exhibit impaired movement coordination and increased variability (Ketcham et al., 2002; Lee et al., 2007; Poston et al., 2013; Sleimen-Malkoun et al., 2014).

Musculoskeletal fitness is critical for general health in all adults. Some components of musculoskeletal fitness can predict morbidity and mortality of aging
individuals (Katzmarzyk & Craig, 2002). For example, Vestergaard et al. (2009) found old adults walk more slowly and have greater variation in 20-m lap times during the 400-m walk test. Furthermore, they found a relation between performance in the 400-m walking test and mortality in a group of ~1,000 men and women, aged 65 years and older. Time to complete the 400-m walk, coefficient of variation for 20-m lap time, and the ability to complete the walk were associated with mortality; slower times and more variation in 20-m laps were associated with greater mortality.

Walking speed is also reduced as much as 16% per decade beginning at age 60 yrs (Bohannon et al., 2011; Himann et al., 1988; Oberg et al., 1993). Importantly, walking speed is a significant predictor for activities of daily living (Potter et al., 1995; Shinkai et al., 2000), mobility, cognitive function, and mortality (Rosano et al., 2008; White et al., 2013).

Furthermore, age-related neuromuscular changes have a negative impact on balance (Maki & McIlroy, 1996). Compared with young adults, older adults have larger center of pressure displacements and slower sway velocity when standing with eyes opened or closed (Abrahamova et al., 2008; Hytonen et al., 1993). The reduction in balance in older adults increases the risk of falling and contributes to the decline in mobility and quality of life for these individuals (Rubenstein & Josephson, 2002; WHO, 2012).

Declines in motor function with advancing age are among the first signs of subsequent deterioration in health (Guralnik et al., 1995; Onder et al., 2005). These
changes have consequences for activities of daily living and quality of life. Monitoring age-associated declines in mobility is essential to attenuate the impending health consequences (Ferrucci et al., 2004).

MOTOR AND SENSORY FUNCTION IN MULTIPLE SCLEROSIS (MS)

MS is a neurological disorder that affects approximately 400,000 people in the US, with around 200 new cases each week (http://www.nationalmssociety.org). This neurological disorder is mainly due to myelin loss that reduces signal transmission and processing within the nervous system. Common symptoms reported in the first year of the disease include sensory impairment, fatigue, reduced mobility, and declines in hand function (Kister et al., 2013). The prognosis varies among patients (Confavreux et al., 2006), but invariably involves progressive muscle weakness (Guclu-Gunduz et al., 2012; Chen et al., 2007), difficulties with mobility, and reductions in the ability to perform activities of daily living, which all reduce quality of life (Bakshi, 2003; Hemmett 2004; Motl et al., 2011; Sutliff, 2010; Yozbatiran et al., 2006). Approximately 50% of individuals with MS need mobility aids within the first 15 years of the disease (Aronson, 1997; Hadjimichael et al., 2008; Pugliatti et al., 2008; Stuifbergen et al., 2006).

Sensory symptoms are observed in approximately 70% of individuals with MS (Rae-Grant et al., 1999). Sensory symptoms manifest in different forms and can include paresthesia, tactile hypoesthesia, or anesthesia (Sanders & Arts, 1986). Persons with MS often report numbness, tingling, or the sensation of pins-and-needles in one limb. The onset of these symptoms varies, but 39% of individuals
with MS exhibit these symptoms in the early stages of the disease (Paty, 2000; Burks & Johnson, 2000).

Mobility in MS

According to the National Multiple Sclerosis Society, mobility is the ability to get anywhere you need to go easily and safely within the energy drain limit (http://www.nationalmssociety.org/Living-Well-With-MS/Mobility-and-Accessibility). Most individuals with MS (83%) have mobility limitations that range from moderate to severe within 30 years after the onset of the disease (Weinshenker et al., 1989, 1994). The rate of decline in mobility varies with the type of MS. For example, persons with progressive MS will have mobility impairment within the first five years (Weinshenker et al., 1989). One of the most important goals in rehabilitation is to improve mobility, especially gait (Kalb 1996; Mertin 1994; Schapiro 1994). This is accomplished by first analyzing gait performance and then implementing corrective exercises and education on how to use mobility devices (Chan, 1999, 2000).

Individuals with MS walk more slowly, spend more time in the double-support phase, walk with wider strides, and consume more oxygen when trying to walk at the same speed as healthy individuals (Motl & Pilutti, 2012a, Remelius et al., 2012). The changes in gait for individuals with MS are associated with reductions in walking performance when tested on both short and long walking tests (Kieseier et al., 2012; Pilutti et al., 2013). These tests are strongly associated with patient-
reported measures of ambulation and fatigue (Gijbels et al., 2010; Goldman et al., 2008; Motl et al., 2013; Savci et al., 2005).

**Sensory Function in MS**

There is a constant progression of sensory impairments in MS (Zackowski et al., 2014). This sensory loss is associated with a higher dependence on vision for mobility and postural control, and visual information processing time is increased to compensate for sensory loss (Heenan et al., 2014). Individuals with MS sway more during upright standing and are significantly weaker than healthy controls, which is associated with a decrease in the sensitivity of cutaneous receptors (Zackowski et al., 2014). As cutaneous sensation decreases in the foot, balance declines (Brown & Metz, 2005). For example, balance during upright standing is more easily disturbed in individuals with somatosensory loss (e.g., proprioception impairment) (Rougier et al., 2007). Furthermore, sensory tests, such as the two-point discrimination sensation test on the heel and vibration sensation test on the first metatarsal of the foot, can predict performance on tests of standing balance (Citaker et al., 2011). The statistical model reported in this study explained 47.6% of the variance in the duration of one-leg standing balance in persons with MS.

This increases the mobility risk, especially falling, and energy demand (Cattaneo et al., 2002; Horak et al., 2001; Rougier et al., 2007). Sensory deterioration, therefore, negatively impacts the mobility of persons with MS. Treatment is not typically administered for declines in sensation unless the sensory symptoms interfere with the person’s ability to function (http://www.nationalmssociety.org/).
More emphasis needs to be placed on the influence of changes in sensory function on motor function (e.g., mobility) and the ways to restore sensation for individuals with MS.

The declines in physical function can be partially restored by exercise training, but the restorative capacity of treating the sensory deficits has received insufficient attention (Barrett et al., 2009; Baudry et al., 2011; Sandroff et al., 2013, Snook et al., 2009).

**MANUAL DEXTERITY AS AN INDEX OF MOTOR FUNCTION**

Manual dexterity is described as the ability to manipulate an object through skillful coordination of the hands and fingers and is a key indicator of motor function (Gershon et al., 2010). It combines elements of mental acuity, tactile sensibility, training, strength, and force steadiness. Manual dexterity is required for numerous activities of daily living, such as grooming, writing, and cooking. In young adults, manual dexterity is an indicator of performance for some professional jobs, such as musicians, dentists, and surgeons (Lundergan et al., 2007). Manual dexterity declines in healthy aging and with certain diseases, which can make activities of daily living even more challenging (Seidel et al., 2002, 2009; Williams et al., 1982; Wiesendanger & Serrien, 2001).

**Hand Function in Older Adults**

Studies have shown an average increase in movement time for tests of manual dexterity—worse performance—of ~60% in older adults compared with young adults (Welford, 1977). Moreover, older individuals take longer to perform handwriting.
(Amrhein & Theios, 1993; Carnahan et al., 1998), reach and grasp, (Bennett & Castiello, 1994), and point-to-point movements (Cooke et al., 1989; Goggin & Meeuwsen, 1992; Ketcham et al., 2002).

At least 18 different tests are available to measure manual dexterity. The NIH Toolbox test to quantify manual dexterity is the nine-hole pegboard test (9HPT). It is a well-established and validated test commonly used in clinical trials and physiological studies (Fischer et al., 1999; Goodkin et al., 1988; Mathiowetz et al., 1985; Oxford et al., 2003). The outcome of this test is the time required for the subject to insert and remove nine cylindrical pegs from a board as quickly as possible. The average time to complete the 9HPT varies based on the age of the person: 49 ± 13 s (mean ± SD) for 3-yr-olds, 19 ± 3 s for 18 to 29-yr-olds, and 24 ± 6 s for 70 to 85-yr-olds (Kallen et al., 2012). It is not routinely used in a clinical setting, largely because completion times for this test are relatively insensitive to the decline in manual dexterity exhibited by middle-aged and older adults (Yancosek & Howell, 2009).

The grooved pegboard test (GPT) is a more sensitive test that has 25 randomly oriented slots and requires the subject to place key-shaped pegs into grooved holes as quickly as possible (Marmon et al., 2011a, 2011b; Thompson-Butel et al., 2014; Wang et al., 2011; Almuklass et al., 2016a, 2016b). This test requires visuomotor coordination, which most dexterity tests lack (Bryden & Roy, 2005). This feature makes the test unique and has led many clinicians and scientists to include it in neuropsychological batteries (Bryden & Roy, 2005). Also, it is sensitive to sex
differences and handedness (Almuklass et al., 2016a; Bryden & Roy, 2005). In a cross-sectional study of pegboard performance, Marmon et al. (2011b) found GPT completion time was fastest for young adults (59 ± 6 s), slowest for older adults (89 ± 16 s), and intermediate for middle-aged adults (66 ± 9 s). Almuklass et al. (2016a) found that young women (51.7 ± 6.8 s) were significantly faster than young men (56.1 ± 4.9 s) in the GPT completion time.

Grip strength tests are useful for identifying individuals at risk of health deterioration by detecting accelerated reductions in physical function with aging. A longitudinal study by Sasaki et al. (2007) gathered data from ~5,000 participants and found that handgrip strength is the main predictor for all-cause mortality in middle-aged and elderly persons. In another prospective population-based cohort study with mortality surveillance over five years on 919 women (aged 65 to 101 yrs) from the Baltimore, Maryland metropolitan area, handgrip strength was again a strong predictor of total mortality (Rantanen et al., 2003). Furthermore, handgrip strength in middle-age was a predictor of decline in mobility and subsequent disability 25 years later (Rantanen et al., 1999).

Independence in activities of daily living is an optimal goal for every rehabilitation protocol. Hand function is one of the contributors to independence (Rantanen et al., 2002). Task independence includes such activities as dressing, grooming, and housework, which require good coordination and strength of the upper extremities (Lundgren-Lindqvist & Sperling, 1983). Weak hand strength predicts the deterioration in independence and the decline in cognitive ability in
older adults (Taekema et al., 2010). Furthermore, the decline in upper extremity muscle strength and mass (Thompson, 2007; Vidt et al., 2012) in older adults is associated with reduced independence leading to 14% of older adults (65+ yrs) needing assistance with activities of daily living (Fuller-Thomson et al., 2009). Also, hand function is associated with outcomes after hospitalization for older patients (Abizanda et al., 2007).

**Force Steadiness**

Force steadiness is quantified as the fluctuations in force (standard deviation or coefficient of variation) when an individual attempts to maintain a constant force during a brief, submaximal contraction (Galganski et al., 1993). Older adults are less steady when they are asked to maintain submaximal forces as steady as possible compared with young adults (Galganski et al., 1993). Changes in motor unit architecture and rate coding can influence force production during steady contractions (Barry et al., 2007; Enoka et al., 2003; Galganski et al., 1993) and have consequences for hand steadiness in older adults. Studies have found that the peripheral reorganization of motor units, motor unit discharge variability, and common modulation of motor unit activity in both agonist and antagonist muscles contribute to the reduction in force steadiness in older adults (Enoka et al., 2003; Galganski et al., 1993; Laidlaw et al., 2000).

Although some experimental evidence has indicated an association between force steadiness and the variability in discharge times of individual motor units (Laidlaw et al., 2000; Moritz et al., 2005), this has not been a consistent finding
(Barry et al., 2007; Negro et al., 2009; Semmler et al., 2000). Rather, evidence suggests that differences in force steadiness can be explained by the cumulative activity of the involved motor units (Dideriksen et al., 2012; Farina et al., 2010; Semmler et al., 2006). In a demonstration of this association, 74% of the variance in muscle force during steady, low-force contractions was explained by low-frequency modulation (10 Hz) of motor unit discharge times, which was attributed to the common synaptic input received by the motor neurons (Castronovo et al., 2015; Farina & Negro, 2015; Negro et al., 2009). The measurement of force steadiness during such tasks, therefore, provides a quantitative measure of the effective control signal generated by spinal motor neurons (Farina et al., 2016). In addition, findings from computational (Taylor et al., 2002) and experimental (Keenan et al., 2006) studies indicate that differences in force steadiness depend more on the discharge characteristics than the force capacity of motor units (Enoka et al., 2003).

Few studies have investigated the functional significance of reduced force steadiness in manual dexterity across the life span. Ranganathan et al. (2001) showed that older adults who are less steady have longer GPT completion times. Studies conducted in our lab showed force steadiness during index finger abduction and grip strength explained 36% of the variation in GPT completion times among young, middle-aged, and older adults (Marmon et al., 2011b). Similarly, Almuklass et al. (2016a) showed that wrist extension force steadiness and time to match a target during a rapid force-matching task explained 70% of the variance in the GPT for young adults.
Several studies have reported significant associations between measures of force steadiness and motor function. For example, Carville et al. (2007) found the coefficient of variation for force during submaximal isometric contractions (50% of maximum) with the knee extensors was greater for 70-year-olds with a history of falls relative to non-fallers and explained statistically significant amounts of the variance in chair-rise time and stair-climbing power. Similarly, 60 to 85-yr-olds who performed eight weeks of knee extensor steadiness training with moderate loads (30% of maximum) experienced a reduction in the coefficient of variation for force during submaximal isometric contractions (65% of maximum) and improved performance on single-leg balance and timed stair tests (Kobayashi et al., 2014). Also, practice-induced decreases in GPT completion time were significantly correlated with improvements in force steadiness during submaximal contractions with hand muscles (Kornatz et al., 2005; Marmon et al., 2011a).

**Hand Function in MS**

MS causes neurological deficits such as ataxia, apraxia, and diminished sensory function (Kamm et al., 2012; Lassmann et al., 2007; Weinshenker 1994), which are associated with declines in manual dexterity and motor function in persons with MS (Einarsson et al., 2006; Kamm et al., 2012; Sanders & Arts, 1986; Rougier et al., 2007). Impaired hand function is one of the earliest symptoms of MS (Kister et al., 2013; Yozbatiran et al., 2006). Individuals with MS have weaker pinch and handgrip strength than age-matched control subjects (Chen et al., 2007; Guclu-Gunduz et al., 2012); the impairment is often bilateral (Bertoni et al., 2015). MS
also affects hand sensation leading to abnormality in vibration (Sanders & Arts, 1986), light touch-pressure, and two-point discrimination sensations (Cuypers et al., 2010; Guclu-Gunduz et al., 2012). The reduction in light touch-pressure of the thumb and the index finger and the two-point discrimination sensations of the index finger were associated with the impairment in the upper extremity function. Critically, sensory deterioration can negatively impact manual dexterity in persons with MS (Sanders & Arts, 1986; Guclu-Gunduz et al., 2012).

Most people with MS (76%) experience problems with manual dexterity and 44% report problems with activities of daily living (Johansson et al., 2007). Several studies have shown a strong association between hand function and the decline in activities of daily living among individuals with MS (Abbas et al., 2008; Einarsson et al., 2006; Kierkegaard et al., 2012; Rodriguez et al., 1994). Impairment of hand function is associated with disability level and the decline in cognitive function (Yozbatiran et al., 2006). Therefore, impairment of hand function has consequences for the quality of life for individuals with MS (Kierkegaard et al., 2012; Yozbatiran et al., 2006).

Manual dexterity tests are more sensitive to changes in upper extremity function than other methods to quantify disability in MS, such as the Expanded Disability Status Scale (EDSS) (Goodkin et al., 1988). The 9HPT is one of the frequently administered tests to measure hand function in MS (Fischer et al., 1999). The test involves performing two consecutive trials with the dominant followed by two consecutive trials with the non-dominant hand. The average is usually taken.
from the four trials. Average completion times for this test are slower for persons with MS (25.2 ± 10.0 s) than healthy aged-match control subjects (18.0 ± 1.4 s) (Yozbatiran et al., 2006). However, the 9HPT is not used routinely in the clinic. Instead, the more challenging GPT is used for individuals with MS. One of our recent studies found that GPT completion times for persons with MS were slower (107.2 ± 41.7 s) than healthy young (58.0 ± 8.1 s), middle-aged (62.9 ± 14.5 s), and older adults (82.8 ± 18.3 s) (Almuklass et al., 2016b).

**Predictors of Hand Function in Older Adults and Individuals with MS**

Several studies have identified various neuromuscular factors that can predict hand function in healthy older adults and persons with MS. In a cross-sectional study of pegboard performance, for example, Marmon et al. (2011b) found force steadiness during index finger abduction and handgrip strength explained a moderate amount of the variance in GPT completion times ($R^2 = 0.36$). Similarly, Almuklass et al. (2016a) found wrist extension force steadiness and the time it takes to match a target force predict 70% of the variance in GPT completion time for young adults. Moreover, Martin et al. (2015) found hand function in GPT and performance in the game “Operation” were significantly predicted by two measures of hand strength and index finger steadiness. This study also found that age and hand strength significantly predict ($R^2 = 0.46$) hand function. Specifically, age explained more of the variance in line-tracking dexterity and force steadiness, whereas hand strength explained more of the variance in tapping and aiming dexterity. Finally, Ashendorf
et al. (2009) found that three measures of cognitive function explain 21% of the variance in GPT completion time among older adults.

In people with MS, the reductions in light touch-pressure and the two-point discrimination sensations of the thumb and the index finger were associated with the deterioration of upper extremity function in MS patients (Guclu-Gunduz et al., 2012). One of our recent studies on MS has shown that 80% of the delay in the GPT completion time can be explained by the time it takes to select the peg from the well and insert it into the hole (Almuklass et al., 2016b). It also shows the peg-insertion phase accounted for the greatest relative duration of the GPT completion time (Almuklass et al., 2016b).

Although many studies show a strong association between manual dexterity and motor function in aging and MS, few studies have explored the underlying attributes. Identifying the predictor variables that can explain the variance in hand function is critical for the clinical management of declines in dexterity.

**TREATMENT INTERVENTIONS FOR OLDER ADULTS AND INDIVIDUALS WITH MS**

Approaches to restore function are similar for both older adults and individuals with MS. Muscle function can be restored by exercise or applying therapeutic electrical stimulation to supplement reductions in muscle activation (Borde et al., 2015; Hortobágyi et al., 2015; Maddox et al., 2013; Barrett et al., 2009). Among individuals with MS, however, the improvements elicited by exercise training and
therapeutic electrical stimulation are usually limited to those with mild-to-moderate walking disability (Broekmans et al., 2011; Wahls et al., 2010).

**Physical Training Interventions for Older Adults**

Systematic and comprehensive exercises can slow down the reduction in mobility and therefore improve quality of life (Beijersbergen et al., 2013; Hortobágyi et al., 2014; VanSwearingen & Studenski, 2014). The most commonly used rehabilitation approaches are resistance training, balance training, and multimodal exercises (Baker et al., 2007).

Resistance training (contracting against external resistance) is one approach to improve strength, muscle mass, and endurance for elderly adults. The dose, frequency, and duration of the training vary with the exercise and the aim of the training program (Borde et al., 2015). Resistance training in older adults can increase muscle size (Fiatarone et al., 1990; Frontera et al., 1988, 1991), muscle strength (Frontera et al., 1988, 1991; Hunter et al., 2001), and functional ability (Vincent et al., 2002).

Diminished balance increases the risk of falling in older adults, so balance exercises are prescribed to improve postural control (Choi et al., 2015; Howe et al., 2011; Sherrington et al., 2008; Lesinski et al., 2015). Balance training aims to improve the control of posture relative to the body’s base of support. Balance training can include coordination exercises, gait correction, strength training, and eye movement exercises (Choi et al., 2015; Hebert et al., 2011; Howe et al., 2011; Sherrington et al., 2008). Specifically, balance exercises usually begin with training
on a flat surface and later advance to standing with one leg on a cushion ball or unstable surface.

Multimodal exercises are also common in rehabilitation for older adults. Exercise guidelines (ACSM, 1998, 2004) highlight the importance of multimodal exercises that reduce the risk of falling and improve the quality of life for older adults (Baker et al., 2007). Multimodal exercises involve at least three types of modalities, such as endurance, strength, and balance exercises (Baker et al., 2007).

Although, the age-related functional loss occurs first in the lower extremity (Seidel et al., 2009), there is also a decline in upper extremity and hand function with advancing age. Physical training can reduce age-related sarcopenia (Brown et al., 1990; Fiatarone et al., 1990; Frontera et al., 1988, 1991), and increase the strength of the upper extremity (Brown et al., 1990). For instance, upper extremity resistance training for 12-weeks increased in elbow flexor muscle size in older adults with a modest increase in the maximum voluntary contraction force for the elbow flexor muscles (Brown et al., 1990). In another study, Venturelli et al. (2010) found that 6-months of resistance training exercise for the upper extremity increased the functional ability in older adults, thus increasing the activities of daily living by an average of 78%. Specific training for the hand can also improve hand function. Marmon et al (2011a) found that six 25-trial sessions of functional GPT training improved manual dexterity in older adults. Furthermore, Keen et al. (1994) found that 12-wks of strength training the first dorsal interosseus muscle of the dominant hand in older adults improved muscle strength, twitch force, and force
steadiness. Hand-specific training programs for the index finger, can reduce motor unit discharge rate variability, improve force steadiness, and therefore improve manual dexterity in older adults (Kornatz et al., 2005; Laidlaw et al., 1999).

**Physical Training Interventions for MS**

Historically, clinicians often instructed individuals with MS to avoid exercises due to the complication of fatigue and the elevation of core temperature (National MS Society). In 1996, Petajan et al. published a study showing that persons with MS can tolerate and show improvement after participating in an aerobic training program. Since then several clinical studies have shown exercise training is well tolerated by individuals with MS (Aimeta et al., 2006; Fisher et al., 2000; White et al., 2004). Although exercises can be tolerated by these individuals, they are routinely instructed not to perform excessive exercises that may trigger a disease relapse (Gallien et al., 2007).

Compared with healthy subjects, individuals with MS exhibit reduced maximal oxygen consumption (Mostert & Kesselring, 2002; Tantucci et al., 1996), less muscle strength (Carroll et al., 2005; Chen et al., 2007; Lambert et al., 2001; Ponichtera et al., 1992; Schwid et al., 1999), and lower levels of muscle activation (de Haan et al., 2000; Ng et al., 2004; Rice et al., 1992). Consequently, individuals with MS have a relatively high risk of bone-mineral density loss (Cosman et al., 1998; Formica et al., 1997; Nieves et al., 1994) and cardiovascular disease (Brønnum-Hansen et al., 2004). Therefore, tolerable and well-designed exercises are important for persons
with MS and can improve their general health and reduce the risk of complications (Dalgas et al., 2008).

As for older adults, physical training for MS can involve resistance training, endurance training, balance exercises, or combined training (Dalgas et al., 2009). Resistance training can be home-based (DeBolt & McCubbin, 2004) or supervised exercises. Resistance training can moderately increase muscle strength (Aimeta et al., 2006; DeBolt & McCubbin 2004; Taylor et al., 2006; White et al., 2004), improve walking speed (Taylor et al., 2006), and reduce self-reported levels of fatigue (Dodd et al., 2006; White et al., 2004). As little as eight weeks of resistance training can improve muscle strength, power, and endurance, and elicit muscular hypertrophy in individuals with MS (de Souza-Teixeeira et al., 2009). For example, Dalgas et al. (2009) found that 12 weeks of resistance training for the knee extensors improved muscle strength and functional capacity during the 10-m walking test for individuals with MS.

Approximately 90% of individuals with MS report fatigue (Freal et al., 1984). One common approach to reduce fatigue in MS is endurance training (Bjarnadottir et al., 2007; Dalgas et al., 2008). Endurance training has positive effects on both the physiological and psychological profiles for individuals with MS. Several studies have shown that endurance training improves aerobic function as evident by improved maximal oxygen consumption (Mostert & Kesselring, 2002; Petajan et al., 1996; Ponichtera-Mulcare et al., 1997; Rasova et al., 2006; Schulz et al., 2004), muscle strength (Petajan et al., 1996), walking performance (Dettmers et al. 2009),
and some aspects of quality of life, such as depression (Petajan et al., 1996), fatigue (Oken et al., 2004; Rasova et al., 2006; Sutherland et al., 2007), social function (Mostert & Kesselring, 2002; Schulz et al., 2004; Sutherland et al., 2007), and sexual function (Sutherland et al., 2007).

Balance is often impaired in persons with MS, which leads to a greater risk of falls among afflicted individuals (Finlayson et al., 2006). Balance training can involve stability training (Freeman et al., 2010), hippotherapy (the use of horseback riding to train hip and trunk stability) (Bronson et al., 2010), and vestibular exercises (Hebert et al., 2011). For example, Freeman et al. (2010) found that eight weeks of core stability training improved balance and mobility in persons with MS. Similarly, vestibular training improved balance and also fatigue in MS patients (Hebert et al., 2011). Rehabilitation programs targeting sensory function can also improve mobility. Balance exercises supplemented with sensory stimulation, such as vibratory stimulation (Magnusson et al., 1994; Missaoui & Thoumie, 2009; Hebert et al., 2011), have been found to improve mobility and balance in individuals with MS.

Unlike spinal cord injury and stroke, there is no designed rehabilitation protocol to improve hand function in people with MS (Spooren et al., 2012). In MS, muscle strength impairments are distinct, pronounced, and in some patients occur earlier in lower extremities than upper extremities (Schwid et al., 1999; Zackowski et al., 2015). Therefore, most rehabilitation protocols target the lower extremities. However, resistance and endurance training of the upper extremities can improve
their functional capacity (Taylor et al., 2006; Romberg et al., 2004). Specificity of hand rehabilitation is important to improve the outcome, as shown for individuals who have experienced a spinal cord injury or stroke (Spooren et al., 2009, 2012). For example, Ortiz-Rubio et al. (2016) found that an eight-week, home-based intervention program for fine-motor skills of the hand and arm coordination, dexterity, and strength improved hand and arm function in individuals with MS. Hand physical rehabilitation sometimes includes functional training. For instance, playing a musical instrument or constraint-induced movement therapy can both improve hand function in individuals with MS (Gatti et al., 2015; Mark et al, 2008).

**Therapeutic Electrical Nerve Stimulation**

In 1743, Johann Kruger was the first to use therapeutic electrical nerve stimulation to make a paralyzed muscle contract (cited in McWhirter et al., 2015). Since then, numerous experimental and clinical studies have been conducted to investigate the therapeutic significance of electrical stimulation on treating motor, sensory, neurological, and even psychological symptoms. Adjusting the parameters of the electrical stimulation alters the physiological responses, and therefore, the target of the treatment.

**Neuromuscular electrical stimulation (NMES).** NMES is used to restore muscle function by passing current between surface electrodes attached to the skin to generate action potentials in terminal motor axons of a target muscle and thereby evoke an involuntary muscle contraction (Barrett et al., 2009). The current intensity is usually set to a tolerable level (<100 mA), with the stimulus frequency
(40-100 Hz), pulse width (0.2 to 1.0 ms) and shape being modulated to meet specific therapeutic requirements. Multiple sessions of NMES can cause significant changes in muscle and some changes within the nervous system. NMES elicits an increase in the muscular cross-sectional area and peak force produced during isometric contractions (Bezerra et al., 2009; Gondin et al., 2011; Vivodtzev et al., 2012). In addition, NMES improves the responsiveness of reflex pathways, which indicates an improvement in the capacity of the nervous system to activate muscle (Gondin et al., 2006; Jubeau et al., 2006).

NMES has been tested on individuals experiencing mobility limitation caused by progressive diseases, such as chronic obstructive pulmonary disease, chronic heart failure, and cancer (Maddox et al., 2013; Vivodtzev et al., 2012). In these conditions, NMES improves walking endurance, as measured with the 6-min walking test. However, the results of NMES training in persons with MS have been modest and less consistent (Broekmans et al., 2011; Wahls et al., 2010).

Our lab has conducted two studies on the influence of a six-week NMES intervention on walking performance in older adults and individuals diagnosed with MS (Davis et al., 2016; Mani et al., 2016). Preliminary data show improvement in walking endurance after the NMES training in both populations. After 6 wks of NMES, MS patients improved their walking endurance by approximately 10% whereas older adults exhibited improvements in walking endurance, walking speed, strength of the trained muscles, and performance on the chair-rise test.
For many years, NMES has been included in rehabilitation protocols to improve upper extremity function, especially for individuals who have experienced a stroke or spinal cord injury (Baker et al., 1979; Rupp et al., 2012; Quandt & Hummel, 2014). In individuals who have experienced a stroke, NMES can be used in a number of different ways; for example, the non-paretic limb muscle activity can be used to direct the stimulation in a functional pattern for the paretic arm (Knutson et al., 2012). In spinal cord injury, it is used to restore the ability to grasp, hold, and release objects (Rupp et al., 2012).

Sensory electrical stimulation. Rehabilitation programs targeting sensory function can also improve mobility. For example, balance exercises supplemented with sensory stimulation, such as vibratory stimulation of both feet at 100 Hz frequency, bathing in alternately cold and warm water (Missaoui & Thoumie, 2009), and vestibular stimulation (Hebert et al., 2011), have been found to improve mobility in individuals with MS. Improvement in balance and postural control was also observed in stroke survivors after sensory stimulation training that involved vibration devices applied to the calf muscles or with galvanic vestibular stimulation (Magnusson et al., 1994).

Electrical stimulation can also be used to target sensory pathways. Transcutaneous electrical nerve stimulation (TENS) is a sensory stimulation technique with the potential to improve mobility (Armutlu et al., 2003; Sluka & Walsh, 2003).
In MS, the central nervous system develops pathological changes including reductions in the concentration of primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Sensory electrical stimulation can enhance the inhibitory system in the spinal interneuron circuits and facilitate short-term plasticity within spinal inhibitory circuits (Perez et al., 2003). Some studies have shown that sensory stimulation using TENS has helped with muscle spasticity and pain in MS resulting in reducing joint stiffness (Armutlu et al., 2003; Sluka & Walsh, 2003). However, only a few studies have shown that therapeutic sensory electrical stimulation can be used to improve hand function. For example, Cuypers et al. (2010) found that daily one-hour sessions of sensory stimulation using TENS applied over the median nerve for three weeks improved tactile sensitivity of fingers on the dominant hand. In older adults, sensory stimulation for fingertips improves hand tactile acuity and fine motor performance in the hand (Kalisch et al., 2008).

Non-invasive electrical brain stimulation is a potential approach to stimulate sensory nerve fibers in older adults and MS patients with motor-sensory function impairments. Repetitive transcranial magnetic stimulation (rTMS) has been tested in both healthy individuals and persons with neurological disorders (e.g., migraine, depression). The results indicate that it can improve the tactile functions and cause enlargement in the somatosensory cortex (Ragert et al., 2003, 2008; Tegenthoff et al., 2005). A similar technique, transcranial (tDCS) can cause dramatic changes and modulate the functions of somatosensory cortices (e.g., tactile sensation) in healthy subjects and in stroke survivors (Hummel et al., 2005; Ragert et al., 2008;
Rogalewski et al., 2004). This technique was safely used in persons with MS and has helped with tactile sensory loss (Mori et al., 2013).

Rehabilitation exercises aim to improve the impact of disability in old adults and individuals with MS. Physical training and therapeutic electrical nerve stimulation are non-invasive with minimal side effects. Physical exercises can be designed to specifically improve strength, endurance, or balance. Therapeutic electrical stimulation can target the motor or sensory system. However, the sensory system has received inadequate attention given that it has been shown that sensory deterioration can impact mobility.

**SUMMARY**

Motor function declines with advancing age and the progression of MS. The NIH Toolbox comprises a battery of tests that can be used to quantify motor function across the life span in both health and disease. Manual dexterity is one measure of motor function, and a strong predictor of activities of daily living and quality of life. Identifying the neuromuscular determinants that can explain the variance in tests of dexterity and other aspects of motor function (e.g., mobility) will help in managing and promoting motor functions in older adults and persons with MS. Physical exercises and therapeutic electrical nerve stimulation are beneficial for both populations and can slow the decline in motor function and enhance quality of life. Despite a significant role in the decline of motor function, the reduction in sensory function has received inadequate attention as a potential target for
restoring the functional capabilities of both older adults and individuals with such progressive neurological disorders as MS.
CHAPTER II

FORCE STEADINESS AS A PREDICTOR OF TIME TO COMPLETE A
PEGBOARD TEST OF DEXTERITY IN YOUNG MEN AND WOMEN
ABSTRACT

The purpose of the study was to evaluate the capacity of an expanded set of force steadiness tasks to explain the variance in the time it takes young men and women to complete the grooved pegboard test. In a single experimental session, 30 participants (24.2 ± 4.0 yrs; 15 women) performed the grooved pegboard test, two tests of hand speed, measurements of muscle strength, and a set of submaximal, steady contractions. The steadiness tasks involved single and double actions requiring isometric contractions in the directions of wrist extension, a pinch between the index finger and thumb, and index finger abduction. Time to complete the grooved pegboard test ranged from 41.5 to 67.5 s. The pegboard times (53.9 ± 6.2 s) were not correlated with any of the strength measurements or the reaction-time test of hand speed. A stepwise, multiple-regression analysis indicated that much of the variance (R² = 0.70) in pegboard times could be explained by a model that comprised two predictor variables derived from the steadiness tasks: time to match the target during a rapid force-matching task and force steadiness (coefficient of variation for force) during a single-action task. Moreover, the pegboard times were significantly faster for women (51.7 ± 6.8 s) than men (56.1 ± 4.9 s). Participants with slower pegboard times seemed to place a greater emphasis on accuracy than speed as they had longer times to match the target during the rapid force-matching task and exhibited superior force steadiness during the single-action task.
INTRODUCTION

When an individual performs a steady contraction with arm, hand, or leg muscles, the force exerted by the limb is not constant but rather fluctuates about an average value. Force steadiness is a measure of the fluctuations in force (standard deviation or coefficient of variation) when an individual attempts to maintain a constant force during a brief submaximal contraction (Galganski et al., 1993). Findings from computational (Taylor et al., 2002) and experimental (Keenan et al., 2006) studies indicate that differences in force steadiness depend more on the discharge characteristics than the force capacity of motor units (Enoka et al., 2003). Although some experimental evidence has indicated an association between force steadiness and the variability in discharge times of individual motor units (Laidlaw et al., 2000; Moritz et al., 2005), this has not been a consistent finding (Barry et al., 2007; Negro et al., 2009; Semmler et al., 2006). Rather, evidence suggests that differences in force steadiness can be explained by the cumulative activity of the involved motor units (Dideriksen et al., 2012; Farina et al., 2010; Semmler et al., 2006). In a seminal demonstration of this association, Farina and colleagues showed that 74% of the variance in muscle force during steady, low-force contractions could be explained by low-frequency modulation (≤10 Hz) of motor unit discharge times, which was attributed to the common synaptic input received by the motor neurons (Castronova et al., 2015; Farina et al., 2015; Negro et al., 2009). The measurement of force steadiness during such tasks, therefore, provides a quantitative measure of the effective control signal generated by spinal motor neurons (Farina et al., 2016).
Several studies have reported significant associations between measures of force steadiness and motor function. For example, the coefficient of variation for force during submaximal isometric contractions (≤50% of maximum) with the knee extensors was greater for old adults (≥70 yrs) with a history of falls relative to those who had not fallen (Carville et al., 2007) and explained statistically significant amounts of the variance in chair-rise time and stair-climbing power (Seyennes et al., 2005). Similarly, old adults (60-85 yrs) who performed 8 weeks of steadiness training with moderate loads (30% of maximum) experienced a reduction in the coefficient of variation for force during submaximal isometric contractions (≤65% of maximum) with the elbow flexors and knee extensors and improved performance on single-leg balance and ascending and descending stairs (Kobayashi et al., 2014). Moreover, practice-induced decreases in the time to complete a pegboard test of manual dexterity were significantly correlated with improvements in force steadiness during submaximal contractions with hand muscles (Kornatz et al., 2005; Marmon et al., 2011a).

Differences in force steadiness can also explain significant amounts of the variance in performance for some tests of motor function, such as the time to complete the grooved pegboard test. In a cross-sectional study of pegboard performance, Marmon et al. (2011b) found that two predictor variables—force steadiness during index finger abduction and handgrip strength—explained a moderate amount of the variance in pegboard times ($R^2 = 0.36$) exhibited by 75 participants (18-89 yrs). Time to complete the grooved pegboard test was fastest for
young adults (59 ± 6 s), slowest for old adults (89 ± 16 s), and intermediate for middle-aged adults (66 ± 9 s). Within each age group, however, a statistically significant regression model ($R^2 = 0.59$) was only evident for the old adults (75 ± 6 yrs, $n=25$). The model included three predictor variables: age, force steadiness for index finger abduction, and pinch grip strength. The strength and force steadiness data obtained by Marmon et al. (2011b) were not able to explain the variance in times to complete the grooved pegboard test for either the young (26 ± 4 yrs, $n=25$) or middle-aged (51 ± 6 yrs, $n=25$) adults.

The primary purpose of the current study was to evaluate the capacity of an expanded set of force steadiness tasks to explain the variance in the time it takes young adults to complete the grooved pegboard test. Due to previous reports of a sex difference in some tests of manual dexterity (Bowden et al., 2013; Bryden & Roy 2005; Lawrence et al., 2014; Michimata et al., 2008; Ruff & Parker 1993), a secondary purpose of the current study was to compare the pegboard times of men and women. The hypothesis was that a significant amount of the variance in pegboard times for young men and women could be explained by two to three characteristics derived from an expanded set of force steadiness tasks. Moreover, women were expected to exhibit faster times than men to complete the grooved pegboard test (Bryden & Roy 2005; Ruff & Parker 1993).

**METHODS**

Thirty young adults (24.2 ± 4.0 yrs; 15 women) met the inclusion criteria and participated in the study after informed consent was obtained. All subjects were
right-handed (95 ± 10; range: 65-100), as indicated by the Edinburgh Handedness Inventory – Short Form (Veale 2014), free from neurological disease, screened for musculoskeletal abnormalities that could influence upper limb function, and were not taking any medications known to influence neuromuscular or cognitive function. The Institutional Review Board at the University of Colorado Boulder approved the protocol (Protocol # 14-0356).

Each individual enrolled in the study participated in one experimental session that lasted ~2 h. The primary outcome variable was the time to complete a test of manual dexterity (Reuben et al., 2013), the Lafayette grooved pegboard test (Bowden et al., 2013; Thompson-Butel et al., 2014; Wang et al., 2011). The secondary outcome variables included measures of hand speed, muscle strength, and force steadiness to characterize the three latent domains of hand function: strength, coordinated upper extremity function, and sensorimotor processing (Lawrence et al., 2015).

**Grooved Pegboard Test**

The grooved pegboard test required participants to place keyhole-shaped metal pegs into 25 holes on a board as quickly as possible. The holes also have keyhole shapes and are arranged in a 5 x 5 matrix on the board with the orientation of the keyholes varying across the board. The task was to use the right hand to fill the board one hole at a time, beginning from the top left and finishing at the bottom right. Participants practiced the task by inserting pegs into the first row of holes and then performed the test. Performance was quantified as the time taken from a verbal
“Go” signal until the final peg was inserted. Each participant performed the task three times, but the regression analysis was based on the time to complete first trial of the pegboard test as specified in the NIH Toolbox protocol.

Tests of Hand Speed

Due to the possibility that hand speed might influence the time to complete the grooved pegboard test (Bryden & Roy 2005; Ruff & Parker 1993), participants performed two tests to characterize the ability to move the hand rapidly to a prescribed target. A measure of reaction time for hand function was derived from the time it took participants to manipulate the position of a cursor on a screen with a computer mouse. The task involved 25 repetitions (trials) of clicking on a target in the center of the screen and then rapidly clicking on a second target that appeared on the screen after the initial click. The size of the secondary targets varied and they appeared in random order at different locations on the screen. Participants were presented with the same targets, but in a random order. The elapsed time between initial and secondary clicks was measured and averaged across trials to provide the measure of reaction time for this task (Goldberg et al., 2007).

The other measure of hand speed was the time to match the target forces during rapid single- and double-action force steadiness tasks. These force-matching times were specific to the actions required for the expanded set of force steadiness tasks examined in the current study (see section on Force Steadiness). Each trial began with a “Go” signal, similar to that for the pegboard test, and the time taken to
match the target line (5 or 10% of maximal voluntary contraction (MVC) force) was measured offline.

**Muscle Strength**

Due to the significance of muscle strength as a determinant of hand function (Lawrence et al., 2015), the strength of the muscles involved in the pegboard test was characterized with four measures of the peak force exerted during MVCs: handgrip, wrist extension, index finger abduction, and thumb-index finger pinch. Each MVC required the participant to increase force from rest to maximum gradually over a 3 s period and then to maintain the maximal force for ~3 s. Participants were provided with strong verbal encouragement during each MVC trial. Each MVC task involved at least two trials with additional trials performed if the difference in the peak force for the two MVCs was >5%. On average, participants performed 3-4 trials for each MVC task and the peak force was used as the index of muscle strength.
Figure 1. The apparatus used to measure force steadiness during single- and double-action isometric contractions. (A) The task was to move the cursor from its initial position (lower right corner of the monitor) to match the target force (5 or 10% MVC force) and maintain a steady contraction for ~30 s. (B) Example of force traces for wrist extension (top) and thumb-index finger pinch (bottom). (C) The single actions involved wrist extension, index finger abduction, or thumb-index finger pinch, whereas the double actions comprised wrist extension with either index finger abduction or the pinch task.

The four MVC tasks were performed with the right hand and arm while the subject was seated. Handgrip strength was measured by squeezing a dynamometer (Hydraulic Hand Dynamometer, Baseline Evaluation Instruments, Irvington, TX). The other three MVC tasks (wrist extension, index finger abduction, and thumb-index finger pinch) required the participant to place the right hand in a prone position on a cushion with the forearm secured to a metal stand using polyester straps and foam cushioning (Fig. 1). The force exerted during wrist extension was measured with a force transducer (0.0056 V/N, JR3 Model 45E15A-U760-A, Woodland, CA) that was fixed to a rigid restraint aligned with the knuckles (heads
of metacarpals two through five) on the dorsal surface of the hand. The abduction force produced by the index finger was measured with a button force transducer (0.049 V/N, Futek Model LLB130, Irvine, CA) that was placed against the proximal interphalangeal joint. The force generated during the pinch grip was measured by having participants squeeze a similar button force transducer between the thumb and index finger.

*Force Steadiness*

The expanded set of force steadiness tasks required participants to move a cursor displayed on the monitor by performing isometric contractions in the directions of wrist extension, index finger abduction, or thumb-index finger pinch individually (single actions), or a combination of wrist extension with either index finger abduction or the pinch grip (double actions). These specific actions were motivated by the anatomical connections between the compartments of muscles that control digit and wrist actions (Kilbreath et al., 1994; Van Duinen et al., 2009), the distribution of activation signals among the muscles that control digit and wrist actions (Häger-Ross et al., 2000; Paclet et al., 2014; Yu et al., 2010), the interaction between pinch force and wrist actions when transporting a grasped object (Ambike et al., 2013; Werremeyer & Cole 1997), and the influence of wrist movements on cortical projections to the first dorsal interosseus muscle (Gagné & Schneider 2007, 2008).

The steadiness tasks required the participant to match a target force displayed on a monitor placed 1.5 m in front of the seated position. The target force was set at
either 5% or 10% of the MVC force for the prescribed action. The target forces for
the single actions were displayed as either a horizontal (wrist extension) or a
vertical (index finger abduction and pinch) line on the monitor (Fig. 1). The target
for the double actions comprised a circular target located in the middle of the
monitor, which was achieved by performing both actions concurrently. The gain of
the visual feedback was scaled to 20% MVC force in both the vertical and horizontal
directions and participants viewed the monitor while performing the force
steadiness tasks.

After a few practice trials with each of task, participants performed three trials
of each single- and double-action task. The single-action tasks were performed
before the double-action tasks and the order for target force was counterbalanced (5
or 10% MVC) across subjects. The first trial for each steadiness task was used to
measure hand speed during a rapid force-matching task. Participants were
instructed to move the cursor to the target as quickly and accurately as possible and
to maintain a steady force for ~10 s (Fig. 2A). The participant began this trial as
quickly as possible after hearing a “Go” signal from one of the investigators. The
next two trials were used to quantify force steadiness as the coefficient of variation
for force. The instruction was to increase the applied force gradually to match the
target force displayed on the monitor and to exert a steady force for 30 s.
Figure 2. Force trajectories for a single participant during a single-action pinch grip (A), a double-action wrist extension (B), and a double-action pinch grip (C). Time to match the target force was determined by visual inspection performed independently by the four investigators.

The signals recorded by the three force transducers (wrist extension, index finger abduction, and thumb-index finger pinch) were low-pass filtered at 50 Hz.
and sampled at 2000 Hz with an analog-to-digital converter (Power 1401, Cambridge Electronic Design, Cambridge, UK). The force data were obtained with Spike2 data acquisition software (Version 5.20, Cambridge Electronic Design, Cambridge, UK) and stored on a computer for offline analysis.

Data Analysis

Force steadiness was quantified as the coefficient of variation for force over selected segments of each force record (Fig. 1). The selected segment was determined after identifying the point in time when the subject was deemed to have successfully matched the target force. The coefficients of variation for force during the second and third trials of each task were averaged to provide a single measurement of force steadiness for each participant. The timing of the target-matching performance for the test of hand speed was determined from the first steadiness trial when the participants were instructed to reach the target force as quickly as possible. Due to differences in the force trajectory between the single- and double-action tasks (Fig. 2), timing was quantified as the time when the subject first matched the target force (Fig. 2C). Due to the capacity of visual inspection to detect specific events in noisy signals (Jesunathadas et al., 2012), time to match the target force during the rapid force-matching task was determined by independent assessment and agreement of all four investigators.

Within-subject ANOVAs were used to compare the times to match the target force (test of hand speed) and the coefficients of variation for force during the single-
and double-action tasks at the two target forces (5% and 10% of MVC). As a conservative assessment of statistical significance, differences between selected means were examined with the Tukey post-hoc test and Bonferroni corrections. Some means were compared with paired or unpaired t tests. Pearson correlations were used to examine the associations between the time to complete the grooved pegboard test and the secondary outcome variables. Based on the results obtained with the correlation analysis, a backwards, stepwise, multiple-regression analysis was used to construct a model that predicted the variance in the times to complete the first trial of the grooved pegboard test. Multicollinearity was estimated with variance inflation factor (VIF). All statistical procedures were performed with SPSS Statistics (version 22.0; SPSS, Inc., Chicago, IL) with α set at 0.05.

RESULTS

The measurements obtained from 30 participants (15 women) comprised time to complete the grooved pegboard test and assessments of hand-arm strength, hand speed, and force steadiness during submaximal, isometric contractions. Relative to the women, the men were older (25.9 ± 4.7 yrs and 22.5 ± 2.3 yrs, respectively), taller (1.79 ± 0.09 m and 1.67 ± 0.07 m), heavier (774 ± 143 N and 621 ± 87 N), and had a stronger handgrip (511 ± 54 N and 346 ± 46 N). The difference in BMI between the men (24.7 ± 4.7 kg/m2) and women (22.7 ± 4.6 kg/m2) was not statistically significant.

Participants performed three trials of the grooved pegboard test. The third trial (50.0 ± 5.6 s) was significantly (paired t test; P = 0.01) faster than the first trial.
(53.9 ± 6.2 s), but there were no significant differences between the first and second (51.0 ± 5.6 s) trials or the second and third trials. Moreover, women were significantly (unpaired t test: P ≤ 0.05) faster than men for both the first trial (51.7 ± 6.8 s and 56.1 ± 4.9 s, respectively) and the average for all three trials (49.7 ± 6.4 s and 53.5 ± 3.6 s, respectively). Based on the NIH Toolbox protocol for administering a pegboard test of manual dexterity, time to complete the first trial was used in the regression analysis.

There were no statistically significant correlations (P > 0.05) between the time to complete the grooved pegboard test for all participants and any of the strength measurements: handgrip (r = 0.11), wrist extension (r = 0.21), pinch grip (r = 0.03), and index finger abduction (r = 0.10). In addition to men having greater handgrip strength values than women (P < 0.001), their MVC forces were also greater for wrist extension (P < 0.001), pinch grip (P < 0.04), and index finger abduction (P < 0.001).

Time to complete the grooved pegboard test (53.9 ± 6.2 s) was not significantly correlated (r = 0.09) with the time to complete the reaction-time test derived from manipulating a computer mouse (922 ± 79 ms) and there was no difference (P = 0.17) in the reaction times for men (901 ± 67 ms) and women (942 ± 88 ms). As expected, time to match the target force (5 or 10% MVC) during the rapid force-matching task was longer for all three double-action tasks than the single-action tasks, but there were no statistically significant differences between target forces (Table 1).
Table 1. Time to match the target force (s) during rapid single- and double-action steadiness tasks for two target forces.

<table>
<thead>
<tr>
<th></th>
<th>5% target force</th>
<th>10% target force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>2.27 ± 1.42</td>
<td>2.35 ± 1.16</td>
</tr>
<tr>
<td>With pinch</td>
<td>2.92 ± 1.40</td>
<td>4.10 ± 2.59</td>
</tr>
<tr>
<td>With index abduction</td>
<td>4.48 ± 2.50*</td>
<td>5.62 ± 3.30*</td>
</tr>
<tr>
<td>Pinch grip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>1.77 ± 0.90</td>
<td>1.83 ± 0.84</td>
</tr>
<tr>
<td>With wrist extension</td>
<td>2.75 ± 1.23*</td>
<td>2.81 ± 1.16*</td>
</tr>
<tr>
<td>Index finger abduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>1.75 ± 0.58</td>
<td>1.94 ± 0.81</td>
</tr>
<tr>
<td>With wrist extension</td>
<td>2.95 ± 1.13*</td>
<td>2.81 ± 1.19*</td>
</tr>
</tbody>
</table>

Mean ± SD. *P < 0.05 relative to single-action task.

There were statistically significant differences in the coefficients of variation for force during some single- and double-action steadiness tasks (Table 2). For example, it was reduced at the greater target force (10% MVC) for the wrist extensors during the double action with the pinch and during both single- and double-actions for the pinch. Moreover, the coefficients of variation for force were greater during the double-action tasks involving wrist extension and index finger abduction for both target forces. There were no statistically significant sex differences in the coefficients of variation for force across the single- and double-action tasks, except that the values for women (5%: 2.75 ± 0.82%; 10%: 1.91 ±
0.71%) were greater than those for men (5%: 1.88 ± 0.41%; 10%: 1.26 ± 0.20%) when performing the single-action wrist extension at the two target forces.

Table 2. Coefficients of variation for force (%) during steady single or double actions while matching either of two target forces.

<table>
<thead>
<tr>
<th></th>
<th>5% target force</th>
<th>10% target force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>2.32 ± 0.77</td>
<td>1.59 ± 0.61</td>
</tr>
<tr>
<td>With pinch</td>
<td>2.86 ± 0.80</td>
<td>1.91 ± 0.44*</td>
</tr>
<tr>
<td>With index abduction</td>
<td>3.33 ± 1.15†</td>
<td>2.59 ± 1.60†</td>
</tr>
<tr>
<td>Pinch grip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>4.14 ± 2.10</td>
<td>2.79 ± 1.34*</td>
</tr>
<tr>
<td>With wrist extension</td>
<td>4.83 ± 1.90</td>
<td>3.47 ± 1.34*</td>
</tr>
<tr>
<td>Index finger abduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>2.72 ± 1.15</td>
<td>1.94 ± 1.08</td>
</tr>
<tr>
<td>With wrist extension</td>
<td>5.82 ± 4.84†</td>
<td>5.20 ± 4.41†</td>
</tr>
</tbody>
</table>

Mean ± SD. *P < 0.05 relative to 5% target force. †P < 0.05 relative to single action.

To identify candidate variables to be included in the multiple-regression analysis, correlations were examined between time to complete the grooved pegboard test and the measures of force steadiness (coefficient of variation for force) and the hand-speed test of time to match the target force during the first steadiness trial of each task. The only statistically significant correlation between the pegboard times and coefficient of variation for force was the single-action wrist extension task to a target force of 10% MVC (Table 3). The negative correlation indicated that
longer times to complete the pegboard test were associated with lesser values for the coefficient of variation for force.

**Table 3.** Pearson correlation coefficients between pegboard times and the coefficient of variation for force during the single- and double-action steadiness tasks.

<table>
<thead>
<tr>
<th></th>
<th><strong>5% target force</strong></th>
<th></th>
<th></th>
<th><strong>10% target force</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 30)</td>
<td>Men (n = 15)</td>
<td>Women (n = 15)</td>
<td>All (n = 30)</td>
<td>Men (n = 15)</td>
<td>Women (n = 15)</td>
</tr>
<tr>
<td>Wrist extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>-0.137</td>
<td>-0.111</td>
<td>0.163</td>
<td>-0.470</td>
<td>-0.399</td>
<td>-0.366</td>
</tr>
<tr>
<td>With pinch</td>
<td>-0.135</td>
<td>-0.178</td>
<td>0.063</td>
<td>-0.155</td>
<td>-0.170</td>
<td>-0.070</td>
</tr>
<tr>
<td>With index abduction</td>
<td>-0.072</td>
<td>-0.106</td>
<td>0.183</td>
<td>-0.155</td>
<td>0.141</td>
<td>-0.116</td>
</tr>
<tr>
<td>Pinch grip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>-0.057</td>
<td>-0.223</td>
<td>0.196</td>
<td>0.194</td>
<td>-0.001</td>
<td>0.488</td>
</tr>
<tr>
<td>With wrist extension</td>
<td>0.068</td>
<td>0.005</td>
<td>0.237</td>
<td>0.027</td>
<td>-0.140</td>
<td>0.273</td>
</tr>
<tr>
<td>Index finger abduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>-0.156</td>
<td>0.083</td>
<td>-0.122</td>
<td>-0.101</td>
<td>0.104</td>
<td>-0.115</td>
</tr>
<tr>
<td>With wrist extension</td>
<td>-0.029</td>
<td>-0.111</td>
<td>0.101</td>
<td>-0.033</td>
<td>0.044</td>
<td>-0.020</td>
</tr>
</tbody>
</table>

Bold font indicates statistically significant (P < 0.05) correlation coefficients.
Table 4. Pearson correlation coefficients between pegboard times and the time to match the target force during the rapid single- and double-action steadiness tasks.

<table>
<thead>
<tr>
<th></th>
<th>5% target force</th>
<th>10% target force</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 30)</td>
<td>Men (n = 15)</td>
</tr>
<tr>
<td>Wrist extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>0.040</td>
<td>0.431</td>
</tr>
<tr>
<td>With pinch</td>
<td>0.044</td>
<td>0.351</td>
</tr>
<tr>
<td>With index abduction</td>
<td>0.200</td>
<td>0.047</td>
</tr>
<tr>
<td>Pinch grip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td>-0.006</td>
<td>0.138</td>
</tr>
<tr>
<td>With wrist extension</td>
<td><strong>0.451</strong></td>
<td>0.487</td>
</tr>
<tr>
<td>Index finger abduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single action</td>
<td><strong>0.514</strong></td>
<td><strong>0.604</strong></td>
</tr>
<tr>
<td>With wrist extension</td>
<td>0.121</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Bold font indicates statistically significant (P < 0.05) correlation coefficients.

In addition, the pegboard times were significantly correlated with the hand-speed tests of time to match the target force during the double-action pinch task (5 and 10% MVC force) and the single-action index finger abduction task (5% MVC force; Table 4). Moreover, the correlation coefficients were statistically significant at the greater target force (10% MVC) for both men and women during the double-
action pinch task, but only for men during the single-action index finger abduction task at both target forces (5% and 10% MVCs). The mean ± SD for the time to match the pinch target force (10% MVC) during the double-action task was 2.81 ± 1.18 s and the difference between men (2.97 ± 1.2 s) and women (2.64 ± 1.2 s) was not statistically significant (P = 0.45). The statistically significant correlations in all instances were positive, indicating that slower pegboard times were associated with longer times to match the target during the rapid force-matching task.

The variables that were significantly correlated with the pegboard times were entered into the stepwise, multiple-regression analysis. The analysis converged on a model with two significant predictor variables: time to match the 10% MVC force during the rapid double-action pinch task (partial r = 0.78; VIF = 1.06) and the coefficient of variation for force during single-action wrist extension task (partial r = −0.48; VIF = 1.06). The model explained 70% of the variance in the observed times to complete the grooved pegboard test (Fig. 3). Due to the limited number of participants in each group (n = 15), it was not possible to examine the potential determinants of the sex difference in time to complete the grooved pegboard test.
Figure 3. Association between observed and predicted times to complete the grooved pegboard test for young men and women. The predictor variables were identified with a stepwise, multiple-regression analysis and comprised force steadiness during wrist extension (partial r = –0.475) and time to match the pinch-grip target force as quickly as possible during concurrent wrist extension and pinch grip (partial r = 0.780).

DISCUSSION

The main finding of the study was that most of the variance ($R^2 = 0.70$) in the time it took young men and women to complete the grooved pegboard test could be explained by a force-matching test of hand speed and one of the measures of force fluctuations derived from the expanded set of steadiness tasks. In addition, times to complete the test of manual dexterity were faster for women than men.

Predictor Variables

The current study continued the approach of Marmon et al. (2011b) to identify the neuromuscular characteristics that could explain the variance in pegboard times for young adults. Consistent with the previous results, the pegboard times for the
young adults were not related to the strength of key muscles (handgrip, wrist extensors, pinch grip, and index finger abductors) involved in the test of manual dexterity. Moreover, there was no significant association between the pegboard times and the speed with which the participants could manipulate a computer mouse in a reaction time test.

Rather, the two significant predictor variables to emerge in the current study were derived from the force steadiness tasks. The strongest predictor was the time to match the pinch target force during the rapid double-action task (Fig. 2C), which provides a functional assessment of known interactions between the muscles that control digit and wrist actions (Ambike et al., 2013; Gagné & Schneider 2007, 2008; Häger-Ross & Scheiber 2000; Kilbreath & Gandevia 1994; Paclet et al., 2014; Van Duinen et al., 2009; Werremeyer & Cole 1997; Yu et al., 2010). The results indicate that the ability to match 10% MVC force with pinch grip while concurrently contracting the wrist extensors to the same target force provided a statistically significant prediction of the time to complete the grooved pegboard test. None of the other single- or double-action tasks to either target force was as strongly associated with performance on the test of manual dexterity.

As indicated by the force trajectories in Figure 2, the strategy used to reach the target as quickly as possible during the double-action steadiness tasks was not simply a measure of the maximal rate of force development (Fig. 2A), but typically (25 of the 30 participants) involved several minor adjustments in the applied force (Figure 2C). The capacity to match a target force during such isometric contractions
appears to depend on the extent to which an individual can modulate the discharge rate of the activated motor units. For example, the ability to match a varying target force with an abduction force exerted during an isometric contraction by the index finger improved after 15 practice trials and was accompanied by a reduction in the variability (standard deviation and coefficient of variation) of the interspike intervals for motor units in the first dorsal interosseus muscle (Knight & Kamen 2004). Participants who took longer to match the pinch target force (10% MVC) during the double-action task may have employed more variable discharge rates during the rapid force-matching task.

The other significant predictor variable in the current study was the coefficient of variation for force during the single-action steadiness task with the wrist extensors when matching the 10% MVC target force. The emergence of this predictor variable is consistent with the known influence of wrist actions on pinch forces when transporting a grasped object (Ambike et al., 2013; Werremeyer & Cole 1997). Contrary to expectations, however, the correlation coefficient was negative, which indicated that the participants with lower coefficients of variation for force during this task took longer to complete the grooved pegboard test. The reason to expect a positive association between these two variables is that greater values for the coefficient of variation for force indicate a reduced ability to perform accurate movements (Chen et al., 2012; Christou & Enoka 2011; Christou et al., 2003; Poston et al., 2010), such as retrieving pegs and inserting them into holes. In contrast, the
current findings indicate that the measure of force steadiness was inversely related to performance of young adults on the test of manual dexterity.

If the amplitude of the force fluctuations during steady contractions does provide a surrogate index of the effective control signal generated by spinal motor neurons (Farina et al., 2016), the results of the current study suggest that the proportion of common synaptic input varied across some of the force steadiness tasks that were examined. The coefficient of variation for force, for example, decreased with target force for three of the seven single- and double-action tasks and increased during the double-action task relative to the single-action task involving index finger abduction (Table 2). There were no statistically significant group differences in the coefficients of variation for force derived from the other tasks, including the single-action wrist extension task that produced one of the two significant predictor variables. Nonetheless, those young adults who took longer to complete the pegboard test exhibited lower values for the coefficient of variation for force during the single-action wrist extension task, which suggests that they achieved the target force (10% MVC) during this task with a lesser proportion of common synaptic input.

Consistent with this interpretation, Castronovo et al. (2015) reported no statistically significant differences in either the coefficient of variation for dorsiflexor force or the estimated proportion of common synaptic input during steady contractions at two target forces (20 and 50% MVC).

Although the two significant predictor variables ultimately depend on the discharge characteristics of the activated motor units, this activity can be
modulated by the relative emphasis on speed and accuracy when manipulating the pegs. Despite the requirement to complete the pegboard test as quickly as possible, the tradeoff between speed and accuracy when moving each peg may result in individuals who value accuracy above speed taking longer to complete the test of manual dexterity (Endrass et al., 2012, Forstmann et al., 2011, Nagengast et al., 2011). A participant who placed a greater emphasis on accuracy, for example, would have taken longer to perform the rapid force-matching task and would have exhibited a lower coefficient of variation for force during the wrist-extension task when attempting to match the target as closely as possible. The variance in times to complete the grooved pegboard test for young adults, therefore, seems to be explainable in terms of the speed-accuracy tradeoff (Carlton 1994; Zelaznik et al., 1988). Why an individual chooses to emphasize speed or accuracy when making decisions about movement strategies during such tasks may be related to their attitude toward risk (O’Brien & Ahmed 2016; Wolpert & Landy 2012).

**Sex Difference in Pegboard Times**

Consistent with some prior studies (Bryden & Roy 2005; Ruff & Parker 1993), the current study found that young women were able to complete the grooved pegboard test (pegs: 3-mm diameter) more quickly than young men. Faster times have been reported for women aged 16-54 yrs, but not for women aged 55-70 yrs (Ruff & Parker 1993). Moreover, women (18-39 yrs) are faster than men independent of handedness and the hand used to perform the pegboard test (Bryden & Roy 2005; Michimata et al., 2008). Similarly, Michimata et al. (2008) found that young women
(20-39 yrs) were able to place more pegs (3-mm diameter) into a 20-hole pegboard in 30 s than young men. Normative data for the NIH Toolbox, however, indicate no sex difference in the time to complete the 9-hole pegboard test, which involves pegs that are 6.4 mm in diameter (Kallen et al., 2012). Despite these different results with variation in peg size, the faster times for women do not seem to be attributable to differences in hand size (Sivagnansunderam et al., 2015).

In contrast, men (three groups: 16-39, 40-54, and 55-70 yrs) are able to perform a greater number of finger taps in 10 s (52.8 ± 5.9, 54.3 ± 5.7, and 53.5 ± 6.4 taps, respectively) than matched groups of women (49.3 ± 4.6, 47.0 ± 5.6, and 45.7 ± 5.5 taps, respectively) (Ruff & Parker 1993). Similarly, there was a trend (P = 0.09) for young men (20-35 yrs) to achieve a greater pinch force (177 ± 33 g) than young women (155 ± 44 g) when compressing an unstable spring in a strength-dexterity test (Lawrence et al., 2014). These findings demonstrate that sex differences in manual dexterity depend on the test used to quantify the index of motor function (Bowden et al., 2013).

Despite these several reports indicating that young women exhibit faster times for the grooved pegboard test than young men, the underlying mechanisms are largely unknown. Unfortunately, the sample sizes in the current study (n = 15 in each group) were too small to perform a multiple-regression analysis that might identify neuromuscular characteristics that could explain the variance in the pegboard times for men and women separately. Nonetheless, the results do suggest that the approach may be productive with larger sample sizes. For example, both
men and women exhibited statistically significant correlation coefficients between pegboard times and time to match the pinch target force (10% MVC) during the rapid double-action steadiness task (Table 3), which was the strongest predictor variable for both groups combined. However, only the men had a statistically significant correlation coefficient between pegboard times and time to match the target forces (5% and 10% MVC) as quickly as possible during the single-action steadiness task with the index finger (Table 4), which emerged as a significant predictor variable in the study by Marmon et al. (2011b). Although not statistically significant, there were some differences in the correlation coefficients for the two groups, especially between the pegboard times and the times to match the target force for several steadiness tasks (Table 4). Critically, however, the coefficient of variation for force during the single-action wrist extension task—one of the predictor variables—was significantly greater for women, which suggests that the proportion of common synaptic input received by the activated motor neurons during this task was less for men. Whether or not such differences in motor unit activity would contribute to the sex difference in completion times for the grooved pegboard test remains to be determined.

In summary, participants with slower times for the grooved pegboard test had longer times to match a submaximal target force during a rapid double-action pinch task and exhibited superior force steadiness during a single-action wrist extension task. These findings are consistent with known motor unit discharge
characteristics, which were likely modulated by decision-making strategies related to the speed-accuracy tradeoff.
CHAPTER III

PEG-MANIPULATION CAPABILITIES DURING A TEST OF MANUAL DEXTERITY DIFFER FOR PERSONS WITH MULTIPLE SCLEROSIS AND HEALTHY INDIVIDUALS
ABSTRACT

Manual dexterity declines with advancing age and with the development of neurological disorders. The changes in manual dexterity are frequently quantified as the time it takes to complete the grooved pegboard test. The grooved pegboard test requires individuals to manipulate 25 pegs. The manipulation of each peg involves four phases: selection, transport, insertion, and return. The purpose of the study was to compare the times to complete the four phases of peg manipulation and the forces applied to the pegboard during peg selection and insertion in persons with multiple sclerosis (MS) and three age groups of healthy adults. Moreover, multiple-regression models that could explain the variance in pegboard times for each group of participants were compared to assess the relative significance of the peg-manipulation attributes. The performance of 17 persons with MS (52.2 ± 8.3 yrs) was compared with 30 young (24.0 ± 4.4 yrs), 15 middle-aged (46.5 ± 6.5 yrs), and 15 old (70.4 ± 4.0 yrs) adults. The grooved pegboard test was performed on a force plate. Pegboard times for the MS group (104.2 ± 40.3 s) were longer than those for young (55.5 ± 6.7 s), middle-aged (57.5 ± 10.9 s), and old adults (80.6 ± 17.3 s). Regression analysis indicated that the pegboard times for the MS group could be predicted by the time for the peg-selection phase ($R^2 = 0.78$), whereas the predictors for young ($R^2 = 0.33$) and middle-aged ($R^2 = 0.78$) adults were the times for the peg-insertion and return phases, and the predictors for old adults ($R^2 = 0.49$) were the times for the peg-selection and transport phases. The relative influence of peg-
manipulation capabilities on a pegboard test of manual dexterity was greater for persons with MS and middle-aged adults than for young and old adults.

INTRODUCTION

Manual dexterity is the ability to manipulate objects through coordination of the hands and fingers, and is a key indicator of motor function (Gershon et al., 2010; Wang et al., 2011). It combines elements of cognitive acuity, tactile sensation, muscle strength, and force control. Manual dexterity can be quantified as the time to complete a pegboard test, such as the grooved pegboard test or the nine-hole pegboard test.

Tests of manual dexterity are more sensitive to changes in upper extremity function than other methods used to quantify disability in persons with multiple sclerosis (MS), such as the Expanded Disability Status Scale (EDSS) (Goodkin et al., 1988; van Winsen et al., 2010). The most frequently administered pegboard test for persons with MS is the nine-hole test (Alusi et al., 2000; Fischer et al., 1999; Kragt et al., 2006), which requires subjects to insert and then remove nine cylindrical pegs as quickly as possible from nine holes arranged in 3 rows by 3 columns on a board. Average time to complete the nine-hole test is slower for persons with MS (25.2 ± 10.0 s) than for healthy aged-match subjects (18.0 ±1.4 s) (Yozbatiran et al., 2006). Moreover, time to complete the nine-hole pegboard test is strongly correlated with disease-related costs over a six-month period (Koch et al., 2014) and a 20% increase in the time to complete the nine-hole test is associated with a worsening of disability (Kragt et al., 2006). Nonetheless, the greater
discriminative capabilities of the grooved pegboard test might provide more insight into the functional significance of the declines in upper extremity strength and hand sensation associated with the progression of MS (Guclu-Gunduz et al., 2012).

The grooved pegboard test requires greater tactile acuity and visuomotor coordination than the nine-hole pegboard test and provides greater discrimination of dexterity among healthy adults (Wang et al., 2011; Bowden et al., 2013; Bryden and Roy 2005; Thompson-Butel et al., 2014). A study of 75 healthy adults demonstrated that the time to complete the grooved pegboard test is fastest for young adults (mean ± SD: 59 ± 6 s), slowest for old adults (89 ± 16 s), and intermediate for middle-aged adults (66 ± 9 s) (Marmon et al., 2011b). Measures of muscle strength, force steadiness during submaximal isometric contractions, and decision-making strategies explain much of the variance among healthy adults in time to complete the grooved pegboard test (Marmon et al., 2011b; Almuklass et al., 2016a; Hamilton et al., in press). In contrast, essentially nothing is known about how peg-manipulation capabilities contribute to differences in pegboard times between groups of individuals.

The purpose of the current study was to compare the times to complete the four phases of peg manipulation and the forces applied to the pegboard during peg selection and insertion in persons with MS and healthy young, middle-aged, and old adults. Peg-manipulation capabilities were quantified in terms of the times and forces of the four phases associated with inserting individual pegs into the 25-hole pegboard: (1) select one peg; (2) transport it to the specified hole; (3) insert it into
the hole; and (4) move the hand back to the well to obtain another peg. Due to declines in cutaneous sensation exhibited by person with MS (Cuypers et al., 2010; Guclu-Gunduz et al., 2012; Kalron et al., 2013) and old adults (Bowden & McNulty, 2013; Cole et al., 1998; Voelcker-Rehage & Godde, 2010), the hypothesis was that significant amounts of the variance in time to complete the grooved pegboard test for the MS and old groups, but not the young and middle-aged adults, could be explained by peg-manipulation attributes associated with peg selection and insertion.

METHODS

Seventeen persons with MS (52.2 ± 8.3 yrs; 10 women; Patient Determined Disease Steps score 3.6 ± 1.0) and 30 young (24.0 ± 4.4 yrs; 16 women), 15 middle-aged (46.5 ± 6.5 yrs; 8 women) and 15 old (70.4 ± 4.0 yrs; 8 women) healthy adults met the inclusion criteria and participated in the study after informed consent was obtained (Table 1). All procedures were approved by the Institutional Review Board (Protocol #15-0719 for the healthy individuals and Protocol #13-0720 for the persons with MS) and conducted in accordance with the Declaration of Helsinki.
Table 1. Descriptive statistics for the four groups of participants.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age (yrs)</th>
<th>GPT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>17</td>
<td>52.2 ± 8.3</td>
<td>104.2 ± 40.3*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(31-60)</td>
<td>(56.4-202.3)</td>
</tr>
<tr>
<td>Young</td>
<td>30</td>
<td>24.0 ± 4.4</td>
<td>55.5 ± 6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(19-34)</td>
<td>(42.9-71.2)</td>
</tr>
<tr>
<td>Middle-aged</td>
<td>15</td>
<td>46.5 ± 6.5</td>
<td>57.5 ± 10.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(38-59)</td>
<td>(41.2-88.5)</td>
</tr>
<tr>
<td>Old</td>
<td>15</td>
<td>70.4 ± 4.1</td>
<td>80.6 ± 17.3*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(63-79)</td>
<td>(56.7-150.2)</td>
</tr>
</tbody>
</table>

Mean ± SD (range). GPT= grooved pegboard test. *P < 0.05 relative to young and middle-aged, † P < 0.05 relative to old.

All participants performed the tests with the dominant hand, which was determined by self-report for the persons with MS and by the Edinburgh Handedness Inventory – Short Form for the healthy participants (Veale 2014).

Grooved pegboard test. The pegboard was secured to a plate and placed on top of a force transducer (0.0056 V/N, Model 45E15A-U760-A; JR3, Woodland, CA) (Fig. 1A). Force was sampled at 5 kHz, low-pass filtered (second-order bidirectional Butterworth filter, cutoff 12 Hz), and stored on a computer for offline analysis. The force signal was used to determine the time taken for the four phases of each peg manipulation cycle and forces applied to the board when inserting a peg (Fig. 1B). Each subject performed the grooved pegboard test three times with the dominant hand.
Figure 1. Measurement of the times and force applied to the grooved pegboard during a single peg-manipulation phase. A: Pegboard on a force plate. B: An example of the force-time trajectory showing the four peg-manipulation phases: (1) selecting the peg, (2) transporting it to the hole, (3) inserting it into the hole, and (4) moving the hand back to the well. Subjects were instructed to fill the board one row at a time, from left to right (right-handers) or right to left (left-handers) and from top to bottom.

In addition to the grooved pegboard test, the MS participants performed tests of walking endurance and maximal walking speed. Walking endurance was characterized as the distance walked in 6 min when walking around a 160-m track while being encouraged to walk as briskly as possible. Maximal walking speed was measured with two trials of 25-ft walk test, while being encouraged to walk as fast as possible.
Data analysis. A custom MATLAB script (Version 2015a, Mathworks, Natik, MA) was used to determine the force (mean ± SD) applied to the board during peg insertion and the times for the four phases (Fig. 1B). For each trial of the grooved pegboard test, the data were averaged across three sets of pegs (each set comprised 3 pegs: pegs 2-4, 12-14, and 22-24). Due to the absence of statistically significant differences in timing characteristics between the three sets of pegs, the data comprised 51 sets of peg-manipulation measurements for the MS group (n = 17), 90 sets of measurements for young adults (n = 30), and 45 sets of measurements each for middle-aged and old adults (n = 15 in each group).

The Shapiro-Wilk test was used to test for normality. Parametric data were examined with one-way repeated measures analysis of variance ANOVA to assess differences in the timing of phases and forces exerted within each group, and Friedman’s test was used for non-parametric data. The Kruskal-Wallis test was used to assess statistical significance between groups. Due to heteroscedasticity and unequal sample sizes, the groups were also compared with the Welch and Brown-Forsythe tests. Cohen’s d and Hodges-Lehmann estimators were used to quantify the effect sizes for between-group comparisons. Effect size was quantified by Cohen’s d to indicate differences in standardized means and Hodges-Lehmann statistic estimate to indicate median Cartesian product differences between samples.

Pearson (parametric data) or Spearman (non-parametric data) correlations were used to examine the associations between the time to complete the grooved
pegboard test with the phase times and the force applied to the board during peg insertion. Based on the results obtained with correlation analysis, a stepwise, multiple-regression analysis was used to construct a model that explained significant amounts of the variance in the times to complete the grooved pegboard test for each group. Multicollinearity was estimated with variance inflation factor. Normality tests were performed on the residuals and outliers were removed based on Cook’s Distance criterion (Cook 1977). All statistical procedures were performed with SPSS (version 22.0; SPSS, Chicago, IL) and R (version 3.3.2) with $\alpha$ set to 0.05. Post-hoc comparisons were made with 4 observations, for both within and between groups, which involved 6 statistical comparisons with significance $\alpha$ set to 0.0083.

RESULTS

Results were obtained for 77 individuals distributed across the four groups (Table 1). The data obtained for the MS, middle-aged, and old groups were not normally distributed and were examined with nonparametric tests.

*Grooved pegboard test.* Pegboard times for persons with MS (104.2 ± 40.3 s) and old adults (80.6 ± 17.3 s) were slower ($P < 0.0001$) than those for young adults (55.5 ± 6.7 s), and middle-aged adults (57.5 ± 10.9 s). Persons with MS were also slower ($P = 0.002$) than old adults.

*Phase times.* Persons with MS and old adults were slower than young and middle-aged adults across all four phases, excluding differences ($P = 0.212$, Cohen’s $d = -0.26$, Hodges-Lehmann estimate = -0.07) between middle-aged (0.91 ± 0.27 s) and old (0.98 ± 0.28 s) adults during peg insertion (Table 2). Middle-aged adults
(0.91 ± 0.27 s) were significantly slower \((P < 0.0001, \text{Cohen’s } d = -0.98, \text{ Hodges-Lehmann estimate } = -0.15)\) than young adults \((0.73 \pm 0.13 \text{ s})\) during peg insertion (Table 2, Fig. 2) with no statistically significant differences across any other phase. The MS group \((1.26 \pm 0.44 \text{ s})\) was slower \((P < 0.006, \text{Cohen’s } d = -0.74, \text{ Hodges-Lehmann estimate } = -0.23)\) than old adults \((0.98 \pm 0.28 \text{ s})\) during the peg-insertion phase (Table 2). Within-group analysis identified statistically significant differences between phases for all groups, except between the select \((0.68 \pm 0.23 \text{ s})\) and return \((0.58 \pm 0.18 \text{ s})\) phases for old adults \((P = 0.077)\) (Table 2).

**Figure 2.** Mean ± SE for the times of each for individuals with Multiple Sclerosis (MS) middle-aged adults, and old adults relative to the average values for young adults. Young and middle-aged adults were faster than old adults and persons with MS, except peg-insertion time was not statistically different between middle-aged and old adults. Old adults were significantly faster than the MS group for the peg-insertion phase only. The times for young and middle-aged adults were not statistically different, except middle-aged adults were slower than young adults during peg insertion.

Force during peg insertion. There were no statistically significant differences between groups in the mean force applied to the board during peg insertion.

However, the standard deviation (SD) of force was less for individuals with MS
(0.73 ± 0.31 N) and young adults (0.79 ± 0.51 N) than for middle-aged adults (0.91 ± 0.40 N) (Table 2).
Table 2. Times for the four phases and force applied to the board during peg insertion.

<table>
<thead>
<tr>
<th></th>
<th>Select (s)</th>
<th>Transport (s)</th>
<th>Insert (s)</th>
<th>Return (s)</th>
<th>Force (N)</th>
<th>SD Force (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>0.86 ± 0.39*†</td>
<td>1.04 ± 0.38*†</td>
<td>1.26 ± 0.44*†‡</td>
<td>0.69 ± 0.37*†</td>
<td>1.93 ± 0.98</td>
<td>0.73 ± 0.31†</td>
</tr>
<tr>
<td>Young</td>
<td>0.46 ± 0.13</td>
<td>0.56 ± 0.16</td>
<td>0.73 ± 0.13</td>
<td>0.36 ± 0.10</td>
<td>1.86 ± 1.31</td>
<td>0.79 ± 0.51</td>
</tr>
<tr>
<td>Middle-aged</td>
<td>0.46 ± 0.15</td>
<td>0.53 ± 0.15</td>
<td>0.91 ± 0.27*</td>
<td>0.35 ± 0.10</td>
<td>2.03 ± 0.80</td>
<td>0.91 ± 0.40*</td>
</tr>
<tr>
<td>Old</td>
<td>0.68 ± 0.23*†</td>
<td>0.87 ± 0.36*†</td>
<td>0.98 ± 0.28*</td>
<td>0.58 ± 0.18*†</td>
<td>2.15 ± 1.30</td>
<td>0.92 ± 0.56</td>
</tr>
</tbody>
</table>

Mean ± SD. *P < 0.05 relative to young, †P < 0.05 relative to middle-aged, and ‡P < 0.05 relative to old. Within-group analysis showed there were statistically significant differences between the times for the phases for all groups, except between the select and return phases for old adults (P = 0.077).
Regression models

There were significant correlations between the time for the grooved pegboard test and the timing of the phases for all groups except old adults during the return phase. There were no statistically significant correlations between grooved pegboard time and either mean or SD of force (Table 3).

**Table 3.** Pearson and Spearman correlation coefficients between time to complete the grooved pegboard test with the times for the peg-insertion phases and the force applied during peg insertion.

<table>
<thead>
<tr>
<th></th>
<th>Select (s)</th>
<th>Transport (s)</th>
<th>Insert (s)</th>
<th>Return (s)</th>
<th>Force (N)</th>
<th>SD force (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis (n = 51)</td>
<td>0.79 [0.88]</td>
<td>0.68</td>
<td>0.69</td>
<td>0.77</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Young (n = 90)</td>
<td>0.44</td>
<td>0.36</td>
<td>0.26 [0.36]</td>
<td>0.48 [0.51]</td>
<td>-0.01</td>
<td>-0.1</td>
</tr>
<tr>
<td>Middle-aged (n = 45)</td>
<td>0.46</td>
<td>0.52</td>
<td>0.66 [0.81]</td>
<td>0.49 [0.75]</td>
<td>-0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>Old (n = 45)</td>
<td>0.47 [0.46]</td>
<td>0.43 [0.63]</td>
<td>0.31</td>
<td>0.19</td>
<td>0.05</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Bold font indicates P < 0.05, n = number of trials. Data in brackets denote partial r values for significant predictor variables.

The variables that were significantly correlated with the pegboard times were entered into a stepwise, multiple-regression analysis for each group. Regression analysis revealed a significant model for each group with at least one dependent variable, and the residuals for each model were calculated. Normality tests were then performed on the residuals and outliers were removed when the Cook's
distance was greater than 4/n, where n is the number of trials for the group (10).

Based on this criterion, the number of trials removed from the analysis for each
group was: 4 for MS, 3 for middle-aged and 2 for old. Collinearity was assessed
using the variance inflation factor (VIF).

A regression model for individuals with MS explained 78% of the variance in the
grooved pegboard time with only one predictor variable: peg-selection time (partial r
= 0.88; VIF = 1.00; P < 0.001) (Fig. 3A). Regression analysis for young adults
revealed a model with two predictor variables that explained 33% of the variance in
the grooved pegboard time: peg-insertion time (partial r = 0.36; VIF = 1.01; P =
0.001) and return time (partial r = 0.51; VIF = 1.01; P < 0.001) (Fig. 3B). Regression
analysis for middle-aged adults identified a model with the same two predictor
variables as for young adults, but the two predictors explained 78% of the variance
in the grooved pegboard time: peg-insertion time (partial r = 0.81; VIF = 1.00; P <
0.001) and return time (partial r = 0.75; VIF = 1.00; P < 0.001) (Fig. 3C). A
regression model for old adults explained 49% of the variance in the grooved
pegboard time with two predictor variables: peg-selection time (partial r = 0.46; VIF
= 1.00; P = 0.002) and transport time (partial r = 0.63; VIF = 1.00; P < 0.001) (Fig.
3D).
**Figure 3.** Association between observed and predicted times to complete the grooved pegboard test. 
A: MS individuals. The predictor variables were identified with a stepwise, multiple regression analysis and comprised only one predictor variable: selection phase (partial r = 0.88; VIF = 1.00; P < 0.001). B: Young adults. The predictor variables were identified with a stepwise, multiple regression analysis and comprised insertion phase (partial r = 0.36; VIF = 1.01; P = 0.001) and return phase (partial r = 0.51; VIF = 1.01; P < 0.001). C: Middle-aged adults. The predictor variables were identified with a stepwise, multiple regression analysis and comprised insertion phase (partial r = 0.81; VIF = 1.00; P < 0.001) and return phase (partial r = 0.75; VIF = 1.00; P < 0.001). D: Old adults. The predictor variables were identified with a stepwise, multiple regression analysis and comprised selection phase (partial r = 0.46; VIF = 1.00; P = 0.002) and transport phase (partial r = 0.63; VIF = 1.00; P < 0.001).

To assess the functional significance of the regression model for the MS group, correlations were calculated for the pegboard time and the four peg-manipulation phases with two tests of walking performance (6-min walk and 25-ft walk). As
indicated in Table 4, time to complete the grooved pegboard test was negatively correlated with the distance walked in 6 min (361 ± 140 m) and positively correlated with the time taken to walk 25-ft (8.6 ± 10.6 s). Moreover, the only peg-manipulation phase to be significantly correlated with the two walking tests was peg-selection time, which emerged from the regression analysis as the strongest predictor of the variance in pegboard time for the MS group.

Table 4. Pearson and Spearman correlation coefficients between walking performance tests with time to complete the grooved pegboard test and the times for the four peg-insertion phases.

<table>
<thead>
<tr>
<th></th>
<th>GPT (s)</th>
<th>Select (s)</th>
<th>Transport (s)</th>
<th>Insert (s)</th>
<th>Return (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-min walk test (m)</td>
<td>-0.49</td>
<td>-0.55</td>
<td>-0.21</td>
<td>-0.32</td>
<td>-0.26</td>
</tr>
<tr>
<td>25-ft walk test (s)</td>
<td>0.55</td>
<td>0.65</td>
<td>0.15</td>
<td>0.30</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Bold font indicates P < 0.05.

DISCUSSION

The main finding of the study was that differences in the time to complete a test of manual dexterity—the grooved pegboard test—for four groups of individuals depended on the timing of only one or two of the four peg-manipulation phases. The critical phases overlapped for persons with MS (peg selection) and old adults (peg selection and transport) and were similar for young and middle-aged adults (peg insertion and return time). The proportion of the variance in grooved pegboard time explained by the predictor variables was greater for persons with MS and middle-aged adults (both R²=0.78) than for young and old adults (R² = 0.33 and 0.49, respectively). The results were partially consistent with the hypothesis in that the time it took persons with MS, but not old adults, to complete the grooved pegboard test was negatively correlated with the distance walked in 6 min (361 ± 140 m) and positively correlated with the time taken to walk 25-ft (8.6 ± 10.6 s). Moreover, the only peg-manipulation phase to be significantly correlated with the two walking tests was peg-selection time, which emerged from the regression analysis as the strongest predictor of the variance in pegboard time for the MS group.
test was significantly associated with peg-insertion time. In contrast to the hypothesis, the peg-insertion time for middle-aged adults was more strongly associated with the grooved pegboard time than the peg-selection time of old adults.

The average pegboard time for the MS group was longer than those for the three groups of healthy adults, even though the age of the MS participants (31–60 yrs) overlapped with that for the middle-aged group (38–59 yrs). Others have similarly reported that pegboard times are slower for persons with MS than for healthy individuals (van Winsen et al., 2010; Yozbatiran et al., 2006; Bertoni et al., 2015; Kierkegaard et al., 2012). A consistent finding among studies that have compared the time to complete the grooved pegboard test of different age groups is that old adults are slower than young and middle-aged adults (Wang et al., 2011; Bowden et al., 2013; Marmon et al., 2011b; Hamilton et al., in press; Ruff and Parker 1993).

Despite the similar pegboard times for young and middle-aged adults in the current study, middle-aged adults had greater difficulty inserting the pegs as indicated by a significantly longer peg-insertion phase and greater force fluctuations during peg insertion relative to young adults. The significant difference in peg-insertion times between young and middle aged adults—despite similar pegboard performances—underscores the sensitivity of quantifying the times for each phase.

The relatively low predictive power of the regression models for the pegboard times of young ($R^2 = 0.33$) and old ($R^2 = 0.49$) adults suggests that grooved pegboard performance in these groups depends on factors other than the timing of the four peg-manipulation phases. In the case of young adults, a previous study found that
the primary determinants of grooved pegboard time for young adults were indices of
decision-making strategies related to the speed-accuracy tradeoff \((R^2 = 0.70)\)
(Almuklass et al., 2016a). In contrast, grooved pegboard time for old adults seems to
be constrained by issues related to cognitive function (Hamilton et al., in press; Ashendorf et al., 2009).

Times to complete the four peg-manipulation phases were strongly correlated
with grooved pegboard times for persons with MS (Table 3). Nonetheless, the
regression analysis identified a single predictor variable, time to select each peg
from the well (partial r = 0.88). Peg selection requires the participant to pick up one
of many pegs from the well, which challenges tactile acuity in these individuals.
Persons with MS have impaired light touch-pressure, reduced two-point
discrimination, and impaired vibration sensations of the hand compared with
healthy controls (Guclu-Gunduz et al., 2012; Cuypers et al., 2010). Furthermore,
individuals with MS take longer to complete the Action Research Arm Test, which
measures the ability to handle and transport small and large objects (Carpinella et
al., 2014). Compared with control subjects, persons with MS exhibited less smooth
movements, especially during the manipulation components of the test. The strong
correlations between the times of the four peg-manipulation phases and time to
complete the pegboard test (Table 3) suggest that the deficits in manipulation
responsible for the prolonged peg-selection phase also influenced the times for the
other three phases.
One of the novel findings in the current study is that despite statistically similar pegboard times for young and middle-aged adults, the amount of variance explained the two predictor variables (peg-insertion and return times) differed substantially for the two groups ($R^2 = 0.38$ and 0.78 for young and middle-aged, respectively). Additionally, there were two statistically significant differences in the outcome variables between the two groups: the middle-aged adults took longer to insert pegs and the applied force was more variable (Table 2). The stronger predictor variable for the young adults was the return phase (partial $r = 0.51$), whereas for the middle-aged adults it was the peg-insertion phase (partial $r = 0.81$). The greater predictive power of the regression model for middle-aged adults suggests that their pegboard performance was constrained by functional capabilities. Consistent with this interpretation, Hamilton et al. (in press) found that the grooved pegboard times of middle-aged adults are strongly related to performance during force-matching tasks. These findings suggest that the pegboard times of middle-aged adults are limited by the initial declines in motor function, namely a reduction in the ability to perform steady submaximal contractions (Bronson-Lowe et al., 2013; Martin et al., 2015; Vieluf et al., 2013).

Despite the return phase being the fastest phase with similar times for both the young ($0.36 \pm 0.10$ s) and middle-aged ($0.35 \pm 0.10$ s) adults, it emerged as a predictor variable for both groups. Nonetheless, its explanatory power was greater for middle-aged adults (partial $r = 0.75$) than for young adults (partial $r = 0.51$). The return phase comprises a rapid goal-directed action in which the hand is
displaced from a hole on the pegboard back to the well containing the pegs. The current findings indicate that although the average time to complete this phase was similar for young and middle-aged adults, the variance in times for the return phase were more strongly associated (greater partial r value) with the variance in pegboard times for the middle-aged adults than the young adults. This result highlights age-specific differences in the contribution of return phase in manual dexterity.

The two predictors for the grooved pegboard times of old adults were the peg-selection and transport phases. The transport phase, which includes the time from the end of peg selection to the beginning of peg insertion, was the stronger of the two predictor variables (partial r = 0.63). The transport phase is used to detect and align the orientation of the peg held in a pinch between the index finger and thumb to the orientation of the target hole. This task has been reported to require greater tactile acuity and visuomotor coordination than inserting cylindrical pegs for the 9-hole pegboard test (Wang et al., 2011; Thompson-Butel et al., 2014). However, deteriorations in cutaneous sensation and tactile acuity observed in old adults do not appear to explain much of the variance in measures of manual dexterity (Bowden et al., 2013; Hamilton et al. in press; Cole et al., 1998; Voelcker-Rehage et al., 2010). Instead, manipulation of the peg during the transport phase likely relies on various aspects of cognitive function. For example, Ashendorf et al. (2009) reported that the time it took old adults (55-74 yrs) to complete the grooved pegboard test was significantly correlated with scores on tests of psychomotor
function, memory, attention, visuospatial ability, and executive function. An independent component analysis by Hamilton et al. (in press) found the grooved pegboard times of old adults (65-89 yrs) to be significantly correlated with age and scores on a test of working memory, but no test of motor function such as those found for middle-aged adults. Consequently, the emergence of time to select a peg as the second predictor variable (partial r = 0.46) for the pegboard times of old adults may be related to a decline in working memory (Hamilton et al. in press).

In conclusion, times to complete the four peg-manipulation phases during the performance of the grooved pegboard test were all significantly correlated with the time to complete the pegboard test for all four groups of participants, except for the return phase of old adults. Moreover, the variance in grooved pegboard times for each group of participants could be explained by the timing of one or two of the peg-manipulation phases. Despite some similarities across groups in the identified explanatory variables, the predictive power of the regression models was stronger for the MS group and middle-aged adults than for young and old adults. These findings indicate that age- and health-related decreases in performance on tests of manual dexterity are attributable to the progressive decline in several different aspects of sensorimotor processing.
CHAPTER IV

NEUROMUSCULAR AND CLINICAL CORRELATES OF WALKING PERFORMANCE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS
ABSTRACT

Objective: To examine the associations between neuromuscular characteristics of lower leg muscles and clinical assessments of physical function with walking performance of individuals who are moderately disabled by multiple sclerosis (MS).

Methods: In 1-3 data collection sessions that were separated by 4-6 wks, 23 individuals with relapsing-remitting MS (53.4 ± 7.3 yrs) participated in the study. Evaluation sessions comprised tests of walking (25-ft walk and 6-min walk), manual dexterity, health-related questionnaires, and strength, force steadiness, and motor unit discharge assessments of lower leg muscles. The analysis compared the discharge characteristics of motor units in the medial gastrocnemius, lateral soleus, and tibialis anterior. Multiple-regression analyses were used to construct models to explain the variance in measures of walking.

Results: There were significant differences (effect sizes: 0.21 to 0.60) between the three muscles in mean interspike interval (ISI) and ISI distributions during steady submaximal contractions with the plantar flexor and dorsiflexor muscles. The regression models, based on neuromuscular characteristics, explained 40% of the variance in the 6-min walk distance and 47% of the variance in 25-ft walk time. The regression models that included the clinical assessments explained 63% of the variance in the 6-min walk distance and 47% of the variance in 25-ft walk time.

Conclusion: Moderate amounts of the variance in two tests of walking performance were explained by the neuromuscular characteristics of lower leg muscles. The two
walking tests were also significantly associated with a self-reported assessment of disability status and the time to complete the test of manual dexterity.

**INTRODUCTION**
Multiple sclerosis (MS) is a debilitating neurological disorder that invariably leads to difficulties with mobility, decreases in manual dexterity, declines in daily levels of physical activity, and reductions in quality of life (Heesen et al., 2008; Kos et al., 2008; Motl et al., 2011a; Sutliff 2010). The progressive impairment of mobility typically results in ~50% of afflicted individuals requiring walking aids within 15 years of disease onset (Baert et al., 2014; Hadjimichael et al., 2008; Klassen et al., 2008; Larocca 2011; Motl et al., 2011b; Pugliatti et al., 2008; Stuifbergen et al., 2006). Moreover, decreases in walking performance are accompanied by declines in manual dexterity that constrain upper body function (Drake et al., 2010; Kierkegaard et al., 2012; Yozbatiran et al., 2006).

Gait analyses indicate that persons with MS prefer slower walking speeds, spend more time in the double-support phase, walk with wider strides, and consume more oxygen to walk at the same speed as healthy control subjects (Motl et al., 2012b; Remelius et al., 2012). The adaptations in gait exhibited by individuals with MS are associated with declines in performance on both short- (25 ft, 10 m, and 30 m) and long-distance (100 m, 2 min, and 6 min) walk tests (Baert et al. 2014; Goldman et al., 2013; Kieseier & Pozzilli 2012; Pilutti et al., 2013). The short-distance walk tests are used clinically to indicate walking disability, whereas the long-distance walk tests provide a measure of walking endurance and functional
capacity (Cohen et al., 2014; Coleman et al., 2012; Goldman et al., 2013; Kieseier & Pozzilli, 2012; Sandroff et al., 2015). Moreover, tests of walking endurance, such as the 6-min walk, are strongly associated with patient-reported measures of ambulation and fatigue (Gijbels et al., 2010; Motl et al., 2013; Savci et al., 2005).

The reductions in walking performance exhibited by persons who are moderately disabled by MS are associated with decreases in other aspects of motor function (Wetzel et al., 2011; Wagner et al., 2014; Kjølhede et al., 2015). For example, maximal voluntary contraction (MVC) torque for the plantar flexors was the most consistent predictor of the variance in 25-ft walk time, 6-min walk distance, and self-perceived limitations in walking (12-item MS Walking Scale: MSWS-12) for 42 individuals with MS (Wagner et al., 2014). Similarly, MVC torque for the knee flexors, but not the knee extensors, emerged as a significant predictor for the variance in 25-ft time and 2-min distance for 52 persons with MS (Broekmans et al., 2012). However, MVC torques for the knee extensors and knee flexors did not explain any of the variance in 6-min walk distance for 24 individuals with MS (Hansen et al., 2014).

Some evidence also suggests that decreases in the ability to control force during submaximal contractions is associated with declines in mobility for persons with MS. For example, Davies et al. (2017) found significant correlations between accuracy when matching a sinusoidal target by performing isometric contractions with the plantar flexor muscles and several gait variables when individuals with MS walked at a preferred speed. Participants who were less accurate during the
force-matching task exhibited a lesser net torque about the ankle joint at toe-off, shorter step lengths, and slower walking speeds. Similarly, greater force fluctuations during steady contractions with the plantar flexors, when matching a target of 20% MVC torque, were correlated with slower walking speed, slower step rate, and shorter step length in persons with MS (Arpin et al., 2016). Given that most of the variance in force fluctuations during steady contractions can be explained by the common modulation of motor neuron discharge times (Farina & Negro, 2015; Negro et al., 2009), these findings suggest that declines in mobility due to MS are associated with alterations in the activity of the motor units that innervate leg muscles.

The purpose of the current study was to examine the associations between neuromuscular characteristics of lower leg muscles and clinical assessments of physical function with walking performance of individuals who were moderately disabled by MS. There were two hypotheses: 1) significant amounts of the variance in walking performance can be explained by the strength of the plantar flexor muscles and the discharge characteristics of motor units in lower leg muscles during steady submaximal contractions; 2) walking performance is associated with self-reported assessments of walking disability and the time to complete a test of manual dexterity.

**METHODS**

The study enrolled 23 volunteers diagnosed with relapsing-remitting MS (53.4 ± 7.3 yrs; descriptors in Table 1. Key exclusion criteria included history of seizure
disorder, implanted biomedical devices or metal, and skin disease. Twenty-one participants completed a 6-wk intervention with neuromuscular electrical stimulation (NMES) applied to lower leg muscles (Almuklass et al., 2017). These individuals attended 3 evaluation sessions and 18 treatment sessions distributed over 10 wks. Each evaluation session comprised 2 days of testing. The evaluation sessions were performed 1 wk before beginning the 6-wk intervention, within 1 wk after finishing the intervention, and approximately 4 wks after the end of the intervention. The outcomes produced by the intervention are reported in detail elsewhere (Almuklass et al., 2017). Due to the time constraints, the other two participants completed only the initial evaluation session. All participants provided informed consent and the Institutional Review Board at the University of Colorado Boulder approved the protocol (Protocol #13-0720).
Table 1. Descriptive statistics (mean ± SD).

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<table>
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<tr>
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<tbody>
<tr>
<td>Sample size/ women</td>
<td>23/14</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53.4 ± 7.3</td>
</tr>
<tr>
<td>6-min walk (m)</td>
<td>358 ± 135</td>
</tr>
<tr>
<td>25-ft walk (s)</td>
<td>9.4 ± 15.0</td>
</tr>
<tr>
<td>Grooved pegboard (s)</td>
<td>109 ± 40</td>
</tr>
<tr>
<td>PDDS</td>
<td>3.7 ± 1.0</td>
</tr>
<tr>
<td>MFIS</td>
<td>42 ± 20</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>45 ± 11</td>
</tr>
</tbody>
</table>

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<table>
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<tr>
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<tbody>
<tr>
<td>Dorsiflexor MVC torque (N•m)</td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>10.1 ± 6.2</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>14.5 ± 6.7</td>
</tr>
</tbody>
</table>

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<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Plantar flexor MVC torque (N•m)</td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>21 ± 12</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>23 ± 11</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Dorsiflexor steadiness (%)</td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td>6.9 ± 5.5</td>
</tr>
<tr>
<td>20% MVC</td>
<td>6.0 ± 5.2</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar flexor steadiness (%)</td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td>4.1 ± 2.6</td>
</tr>
<tr>
<td>20% MVC</td>
<td>3.4 ± 1.9</td>
</tr>
</tbody>
</table>

Steadiness values are coefficient of variation for force (%).

On the first day of each evaluation session, participants performed walking tests (25-ft walk test and 6-min walk test), a manual dexterity test (grooved pegboard), and completed three health-related questionnaires. Maximal walking speed was measured as the time it took an individual to walk 25 feet as quickly as possible. The average of two trials was used as the measure of maximal walking speed. Walking endurance was characterized as the distance walked in 6 min around a 160-m track. Participants were encouraged to walk briskly, and the distance covered at 1, 2, 4, and 6 min was recorded. Manual dexterity was quantified as the time taken to complete the grooved pegboard test, which required participants to
place 25 pegs into holes on a pegboard as quickly as possible (Almuklass et al. 2016). The health-related questionnaires were the Patient Determined Disease Steps (PDDS), Modified Fatigue Impact Scale (MFIS), and MS Walking Scale-12 (MSWS-12).

On the second day of each evaluation session, muscle strength and force steadiness were measured while the subject lay in a supine position. Muscle strength was quantified as the peak torque (N·m) achieved by the dorsiflexor and plantar flexor muscles of each leg when participants gradually increased muscle torque up to maximum and sustained it briefly. Participants performed 2-5 maximal voluntary contraction (MVC) trials. When two MVC torques were within 10% of each other, the greater value was designated as the MVC torque. Participants then performed submaximal isometric contractions with the dorsiflexor and plantar flexor muscles to match target forces of 10% and 20% MVC torque with the leg the participant identified as experiencing fewer symptoms. The task was to match the target force as steadily as possible during two 30-s trials at each target force with one muscle group at a time. Force fluctuations during each steady contraction were quantified as the coefficient of variation for force and used as a measure of force steadiness.

The force exerted by the limb during the strength and steadiness tasks was measured with a strain-gauge transducer (MLP-300, Transducer Techniques, Temecula, CA). The force signal was low-pass filtered (0–50 Hz; Coulbourn Instruments, Allentown, PA), recorded on a computer, and digitized at 1000
samples/s. All force data were obtained with Spike2 data acquisition software (Version 5.20, Cambridge Electronic Design, Cambridge, UK) and stored on a computer for offline analysis. The recorded force signals were filtered with a 20-Hz low-pass, 2\textsuperscript{nd}-order Butterworth filter to quantify the force fluctuations.

While performing the steadiness tasks with the less affected leg, motor unit activity in the medial gastrocnemius, lateral soleus, and tibialis anterior muscles was recorded with a high-density surface electromyography (EMG) system (4x8 detection points with interelectrode distance of 10 mm). Motor unit activity was recorded during eight steady contractions for each participant: two muscle groups (plantar flexors and dorsiflexors) x two target forces x two trials for each target force. The surface of the skin was prepared and electrodes were placed on the skin over the medial gastrocnemius, lateral soleus, and tibialis anterior muscles (Fig. 1). The EMG electrodes were attached with adhesive pads and tape. Motor unit action potentials were discriminated offline from the EMG recordings with a custom decomposition algorithm (Holobar et al., 2007; Holobar et al., 2010).
Figure 1. Locations of the surface grid electrodes over medial gastrocnemius and soleus (A) and tibialis anterior muscles (B). Selected motor unit action potentials (MUAPs) (C), each column represents 30ms of recording period. Measurement of force steadiness at 10% or 20% MVCs (D).

Data analysis

Due to limitations in automatic decomposition algorithms, the decomposed signals comprised both motor unit activity and waveforms. Each decomposed signal (n = 4,143) was examined and data were deemed artifacts and excluded based on the following criteria, performed in order, derived from previous work in single motor unit discrimination (Barry et al., 2007; Moritz et al., 2005; Pascoe et al., 2013): 1)
discard any interspike interval (ISI) <25 ms or > 400 ms; 2) exclude any motor unit with a coefficient of variation for ISI < 8% or > 55%; 3) reject any motor unit with an ISI distribution that had a skewness value in the range of ± 0.5; 4) eliminate any motor unit that had a coefficient of variation for ISI < 10% and a distribution skewness < 1. In addition, the waveforms of those motor units with coefficients of variation for ISI in the ranges of 8-10% and 50-55% were visually inspected to ensure the identified waveforms were consistent with expected shapes for motor unit action potentials. As a result, 911 decomposed signals were discarded and the analysis was performed on the recordings of 3,232 motor units obtained from the two trials at each target force for the three muscles of the 23 participants.

Differences in the average discharge characteristics (mean ISI, coefficient of variation for ISI, skewness, and kurtosis) across the two trials at each target force indicated that different sets of motor units were recorded during each trial. Nonetheless, some motor units were likely recorded during both trials at each target force (Martinez-Valdes et al., 2017) and perhaps at the two target forces. However, the duplicate recordings were not expected to compromise either the comparison of discharge characteristics across muscles or the regression analysis of functional capabilities. Although each motor unit recording was treated as an independent event in the across-muscle comparison of discharge characteristics, duplicate recordings would not have influenced the between-muscle comparison if there were similar numbers of duplicate recordings at each target force for the three muscles (medial gastrocnemius, soleus, and tibialis anterior), which seems likely
(Martinez-Valdes et al., 2017). Moreover, the regression analysis was based on the average discharge characteristics for all the motor units identified in a single session for each muscle. The average number of motor units recorded in each session (2 trials x 2 target forces) was 38 for tibialis anterior, 18 for gastrocnemius, and 27 for soleus, which resulted in 244 averages that were used in the regression analyses.

The potential influence of duplicate recordings on the average discharge characteristics was estimated by iteratively removing 40% (Martinez-Valdes et al., 2017) of the motor units recorded in the first trial that contributed to an overall mean from all the motor unit means from both trials and comparing it to the mean obtained without the removal of motor units. The procedure was performed on a subset of the motor units (n = 481 motor units) that contributed to the overall mean values for each condition (2 target forces x 3 muscles). Removal of motor units had a minimal influence on the overall mean values. For example, the maximal change in overall mean ISI after 100 iterations of removing 40% of the motor units was 5.77%, with a standard deviation of 2.64 ms. These results suggest that duplicate recordings across trials would not have confounded the outcomes of the regression analysis.

The Kolmogorov-Smirnov (>50 samples) and the Shapiro-Wilk tests (<50 samples) were used to assess normality. The Kruskal-Wallis test was used to compare motor unit characteristics between the three muscles. For the intervention effect, comparisons across time were examined with either one-way repeated-
measures ANOVA (parametric) with a Bonferroni adjustment or Friedman’s test (non-parametric). Post-hoc comparisons with the Kruskal-Wallis test were performed with Dunn’s nonparametric comparisons and significance values were adjusted by Bonferroni corrections for multiple comparisons. The motor unit discharge characteristics for each muscle were compared at the two target forces (10% and 20% MVC) and between trial 1 and trial 2 with the Mann-Whitney U test. The effect size between the three groups was quantified as $\phi$ for non-parametric data, which was obtained from $\left(\frac{\sqrt{x}}{N}\right)$, and as $\eta^2$ for parametric data. The effect size when comparing two values was obtained from $\left(\frac{z}{\sqrt{n_1+n_2}}\right)$.

A spearman correlation was used to examine the associations between the walking performance (25-ft test, 6-min test), clinical assessments (PDDS, MFIS, MSWS-12, grooved pegboard test), and neuromuscular measurements (MVC torque, force steadiness, motor unit discharge characteristics). Based on the correlation analysis, a stepwise, multiple-regression analysis was used to construct models that explained significant amounts of the variance in the 6-min walk (m) and the 25-ft walk (s) tests. Multicollinearity was estimated with variance inflation factor. Normality tests and Cook’s Distance criteria were performed on the residuals and outliers were removed (Cook 1977). All statistical procedures were performed with SPSS (version 24.0; SPSS, Chicago, IL).

**RESULTS**

The data were obtained from 65 experimental sessions that involved 456 successful trials in which force steadiness was measured and 488 successful trials in which
motor units were discriminated during steady isometric contractions. The data for 21 of the participants were obtained during a 6-wk intervention study when measurements were performed before, immediately after, and 4 wks after (retention) the intervention. The intervention improved walking performance for these 21 individuals. The intervention increased the distance walked in 6 min ($P = 0.01$, effect size = 0.25): before = 344 ± 132 m, after = 378 ± 150 m, retention = 386 ± 161 m. Similarly, time to walk 25 ft decreased ($P = 0.001$, effect size = 0.58): before = 10.0 ± 15.6 s, after = 8.8 ± 12.5 s, retention = 8.7 ± 13.4 s. Walking performance at each of the three time points for the 21 participants who completed the intervention was considered as an independent measurement in the current study.

**Motor unit characteristics**

There were modest differences in the discharge characteristics of motor units at the two target forces (Table 2). Mean ISI was briefer at the greater target force (20% MVC) for both tibialis anterior (102 ± 22 and 110 ± 23 ms; effect size = 0.20) and soleus (145 ± 34 and 150 ± 33 ms; effect size = 0.07), but not gastrocnemius (138 ± 36 and 135 ± 34 ms; effect size = 0.06). However, the ISI distributions, as characterized by the coefficient of variation, skewness, and kurtosis, were not significantly different (effect sizes ≤0.06) across target forces for any of the three muscles (Table 2).
Table 2. Motor unit characteristics in tibialis anterior, gastrocnemius, and soleus during steady, isometric contractions at the two target forces.

<table>
<thead>
<tr>
<th></th>
<th>Tibialis anterior</th>
<th>Gastrocnemius</th>
<th>Soleus</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor units (n)</td>
<td>1634</td>
<td>696</td>
<td>902</td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>110 ± 23</td>
<td>138 ± 36*</td>
<td>150 ± 33*†</td>
<td>0.56</td>
</tr>
<tr>
<td>20%</td>
<td>102 ± 22‡</td>
<td>135 ± 34*</td>
<td>145 ± 34*†‡</td>
<td>0.60</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.20</td>
<td>0.06</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>30 ± 13</td>
<td>32 ± 14</td>
<td>30 ± 12</td>
<td>0.06</td>
</tr>
<tr>
<td>20%</td>
<td>30 ± 13</td>
<td>31 ± 13</td>
<td>30 ± 13</td>
<td>0.04</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>ISI distribution skewness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>2.1 ± 1.3</td>
<td>1.6 ± 1.3*</td>
<td>1.6 ± 1.3*</td>
<td>0.26</td>
</tr>
<tr>
<td>20%</td>
<td>2.1 ± 1.2</td>
<td>1.7 ± 1.3*</td>
<td>1.6 ± 1.3*</td>
<td>0.24</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.02</td>
<td>0.05</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ISI distribution kurtosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>12 ± 15</td>
<td>8 ± 11*</td>
<td>9 ± 12*</td>
<td>0.24</td>
</tr>
<tr>
<td>20%</td>
<td>11 ± 13</td>
<td>8 ± 11*</td>
<td>8 ± 11*</td>
<td>0.21</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.02</td>
<td>0.06</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. *P < 0.05 relative to tibialis anterior. †P < 0.05 relative to gastrocnemius. ‡P < 0.05 relative to 10%.
In contrast, there were more substantial differences in discharge characteristics between muscles at the two target forces. Mean ISI was longer at both target forces (effect sizes: 0.56 and 0.60) for gastrocnemius and soleus relative to tibialis anterior and for soleus relative to gastrocnemius (Table 2). Similarly, the ISI distributions differed across muscles as indicated by lesser skewness and kurtosis values (effect sizes: 0.21-0.26) for gastrocnemius and soleus relative to tibialis anterior (Table 2). In contrast, the coefficient of variation for ISI (~30%) did not differ across muscles at either of the target forces (effect sizes: 0.06 and 0.04).

**Associations between walking performance and neuromuscular characteristics**

The distance walked in 6 min was negatively correlated with mean ISI for both soleus (r = -0.46) and gastrocnemius (r = -0.53) during steady isometric contractions with the calf muscles at 10% MVC force (Table 3). The negative correlations indicate that briefer mean ISIs were associated with a greater distance walked in 6 min. In addition, 6-min walk distance was positively correlated with the coefficient of variation for ISI of motor units in gastrocnemius during steady isometric contractions with the calf muscles at 10% MVC (r = 0.47). This association indicates that individuals with greater variability in the ISIs were able to walk further in 6 min (Table 3). The distance walked in 6 min was also significantly correlated with MVC torque for the dorsiflexors in the more affected leg (r = 0.43) and force steadiness of the less effected leg for both the dorsiflexors (r = -0.39) and plantar flexors (r = -0.45) during isometric contractions at 20% MVC force (Table 3). These
associations indicate that the 6-min walk distance was longer for participants with stronger dorsiflexors in the more affected leg and lesser force fluctuations during steady isometric contractions with both the dorsiflexors and plantar flexors in the less affected leg.

The time to walk 25 ft was positively correlated with mean ISI for both soleus ($r = 0.44$) and gastrocnemius ($r = 0.53$) during steady isometric contractions with the calf muscles at 10% MVC force (Table 3). The correlations indicate that briefer mean ISIs were associated with faster times to walk 25 ft. In addition, 25-ft walk time was negatively correlated with the coefficient of variation for ISI of motor units in gastrocnemius during steady isometric contractions with the calf muscles at 10% MVC ($r = -0.44$). This association indicates that individuals with greater variability in gastrocnemius ISIs were able to walk 25 ft more quickly (Table 3). The time to walk 25 ft was also significantly correlated with MVC torque for the dorsiflexors in the more affected ($r = -0.50$) and less affected ($r = -0.34$) legs, MVC torque of the plantar flexors in the more affected leg ($r = -0.34$), and force steadiness for the dorsiflexors ($r = 0.30$) at 20% MVC force and the plantar flexors at both 10% ($r = 0.27$) and 20% ($r = 0.46$) MVC force (Table 3). These associations indicate that the 25-ft walk time was faster for participants with stronger dorsiflexors (both legs) and plantar flexors (more affected leg) and lesser force fluctuations during steady isometric contractions with both the dorsiflexors and plantar flexors.
Table 3. Correlation coefficients between walking tests (6-min walk and 25-ft walk) and neuromuscular characteristics.

<table>
<thead>
<tr>
<th></th>
<th>6-min walk (m)</th>
<th>25-ft walk (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soleus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td>-0.46</td>
<td>0.44</td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td>0.28</td>
<td>-0.21</td>
</tr>
<tr>
<td>20% MVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td>-0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td>0.28</td>
<td>-0.27</td>
</tr>
<tr>
<td><strong>Gastrocnemius</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td>-0.53</td>
<td>0.53</td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td>0.47</td>
<td>-0.44</td>
</tr>
<tr>
<td>20% MVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td>-0.22</td>
<td>0.19</td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td>0.16</td>
<td>-0.16</td>
</tr>
<tr>
<td><strong>Tibialis anterior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td>0.15</td>
<td>-0.14</td>
</tr>
<tr>
<td>20% MVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ISI (ms)</td>
<td>-0.07</td>
<td>0.08</td>
</tr>
<tr>
<td>Coefficient of variation for ISI (%)</td>
<td>0.07</td>
<td>-0.03</td>
</tr>
<tr>
<td><strong>Dorsiflexor MVC torque (N•m)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>0.43</td>
<td>-0.50</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>0.22</td>
<td>-0.34</td>
</tr>
<tr>
<td><strong>Plantar flexor MVC torque (N•m)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>0.22</td>
<td>-0.34</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>0.02</td>
<td>-0.17</td>
</tr>
<tr>
<td><strong>Dorsiflexor force steadiness (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td>-0.26</td>
<td>0.22</td>
</tr>
<tr>
<td>20% MVC</td>
<td>-0.39</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Plantar flexor force steadiness (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% MVC</td>
<td>-0.21</td>
<td>0.27</td>
</tr>
<tr>
<td>20% MVC</td>
<td>-0.45</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Bold font indicates P < 0.05. ISI = interspike interval. Steadiness values are coefficient of variation for force (%).
Associations between walking performance and clinical assessments

The 6-min distance was negatively correlated with the PDDS score ($r = -0.66$), MSWS-12 score ($r = -0.52$), and time to complete the grooved pegboard test ($r = -0.29$) (Table 4). These associations indicate that participants who could walk further in 6 min self-reported lower levels of disability (PDDS and MSWS-12) and completed the grooved pegboard test more quickly.

The 25-ft walk test was positively correlated with the PDDS score ($r = 0.58$), MSWS-12 score ($r = 0.44$), and time to complete the grooved pegboard test ($r = 0.35$) (Table 4). These associations indicate that participants who walked the 25 ft more quickly self-reported lower levels of disability (PDDS and MSWS-12) and took less time to complete the grooved pegboard test.

Table 4. Correlation coefficients between walking tests (6-min walk and 25-ft walk) and clinical measures.

<table>
<thead>
<tr>
<th></th>
<th>PDDS</th>
<th>MFIS</th>
<th>MSWS-12</th>
<th>Grooved pegboard</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-min walk (m)</td>
<td>-0.66</td>
<td>-0.01</td>
<td>-0.52</td>
<td>-0.29</td>
</tr>
<tr>
<td>25-ft walk (s)</td>
<td>0.58</td>
<td>-0.06</td>
<td>0.44</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Bold font indicates $P < 0.05$.

Regression models

Based on the correlation results (Tables 3 and 4), a stepwise, multiple-regression analysis was used to construct models that explained significant amounts of the variance in the 6-min walk distance and 25-ft walk time. Separate models were developed for each walking test based on neuromuscular characteristics or clinical assessments.
Neuromuscular characteristics were able to explain 40% of the variance in the 6-min walk distance with two predictor variables: mean ISI for gastrocnemius when the plantar flexors performed a steady isometric contraction at 10% MVC force (partial $r = -0.48$; VIF = 1.1; $P = 0.006$) and MVC torque for the dorsiflexors of the more affected leg (partial $r = 0.37$; VIF = 1.1; $P = 0.04$) (Fig. 2A). Similarly, neuromuscular characteristics were able to explain 47% of the variance in the 25-ft walk time with three predictor variables: mean ISI for soleus when the plantar flexors performed a steady isometric contraction at 10% MVC (partial $r = 0.51$; VIF = 1.06; $P = 0.005$), MVC torque for the dorsiflexors of the more affected leg (partial $r = -0.43$; VIF = 1.05; $P = 0.02$), and force steadiness when the plantar flexors performed a steady isometric contraction at 20% MVC (partial $r = 0.39$; VIF = 1.04; $P = 0.037$) (Fig. 2B).
Figure 2. Associations between observed and predicted times to complete the two walking tests based on neuromuscular characteristics. A: 6-min walk test. The predictor variables ($R^2 = 0.40$) were mean ISI for motor units in gastrocnemius during a steady contraction at 10% MVC force and the MVC torque for the dorsiflexors of the more affected leg. B: 25-ft walk test. The predictor variables ($R^2 = 0.47$) were mean ISI for motor units in soleus during a steady contraction at 10% MVC force, MVC torque for the dorsiflexors of the more affected leg, and force steadiness for the plantar flexors during an isometric contraction at 20% MVC force.

Clinical assessments were able to explain 63% of the variance in the 6-min walk distance with two predictor variables: PDDS score (partial $r = -0.77$; VIF = 1.07; $P < 0.0001$) and time to complete the grooved pegboard test (partial $r = -0.31$; VIF =
1.07; P = 0.02) (Fig. 3A). Similarly, clinical assessments were able to explain 47% of the variance in the 25-ft walk time with the same two predictor variables: PDDS score (partial r = 0.58; VIF = 1.03; P < 0.0001) and time to complete the grooved pegboard test (partial r = -0.25; VIF = 1.03; P = 0.07) (Fig. 3B).

**Figure 3.** Associations between observed and predicted times to complete the two walking tests based on the clinical measurements. A: 6-min walk test. The predictor variables (R² = 0.63) were PDDS score and time to complete the grooved pegboard test. B: 25-ft walk test. The predictor variables (R² = 0.47) were PDDS score and time to complete the grooved pegboard test.
DISCUSSION

The main findings in the current study were that moderate amounts of variance in the walking performance of persons with MS could be explained by sets of either neuromuscular characteristics or clinical assessments. The explanatory neuromuscular characteristics involved the strength of lower leg muscles, force steadiness during submaximal isometric contractions, and the discharge characteristics of motor units in leg muscles during steady contractions. The predictor variable with the largest partial r values to the two regression models (6-min and 25-ft walk) was the mean ISI for one of the lower leg muscles during steady, isometric contractions at 10% MVC force. The involved muscles were gastrocnemius for the 6-min walk (partial r = -0.48) and soleus for the 25-ft walk (partial r = 0.51), which indicates that longer mean ISIs were associated with worse walking performance: less distance walked in 6 min and longer time to walk 25 ft.

The emergence of gastrocnemius and soleus as significant contributors to walking performance is consistent with part of the first hypothesis that the discharge characteristics of motor units in the plantar flexor muscles can explain some of the variance in walking performance of persons with MS. The discharge characteristics of motor units in the muscles of individuals with neurological disorders, such as MS, Parkinson’s disease, and stroke, tend to exhibit depressed peak discharge rates and lower levels of motor unit recruitment due to alterations in the voluntary activation of the motor neurons (Chou et al., 2013; Glendinning & Enoka 1994; Milner-Brown et al., 1979; Rice et al., 1992; van der Kamp et al., 1995).
Nonetheless, the current report is the first to demonstrate an association between motor unit activity during standardized tasks and performance by individuals with MS on clinical tests of mobility.

In contrast to the first hypothesis, however, it was the strength of the dorsiflexor muscles rather than the planter flexor muscles that had the greater influence on walking performance. The MVC torque of the dorsiflexor muscles in the more affected leg was the second strongest predictor for both the 6-min walk (partial r = 0.37) and the 25-ft walk (partial r = -0.43). This result indicates that stronger dorsiflexors were associated with better walking performance: greater 6-min distance and faster 25-ft time. Among the four significant correlations listed in Table 3 between the strength of lower leg muscles and walking performance, the correlations for MVC torque of the dorsiflexor muscles in the more affected leg were the greatest. This result is consistent with prior reports that the strength of the dorsiflexor muscles is a significant contributor to the disabilities experienced by persons with MS (Benedetti et al., 1999; Thickbroom et al., 2008; Martin et al., 2006; Matsuda et al., 2006). Moreover, increases in the 25-ft walk time with progression of the disease are accompanied by significant decreases in the strength of the dorsiflexor muscles (Zackowski et al., 2015).

The third predictor variable for the 25-ft walk time was force steadiness when the plantar flexor muscles of the more affected leg performed a steady contraction at 20% MVC force. The association (partial r = -0.39) indicated that faster 25-ft times were related to lesser force fluctuations (lower coefficients of variation for force)
during the isometric contraction, which likely indicates less variability in the common modulation of discharge time for motor neurons innervating the plantar flexor muscles during the steady contraction (Farina & Negro, 2015; Negro et al., 2009). This result is consistent with a previously observed correlation for persons with MS between greater force fluctuations during steady contractions with the plantar flexor muscles and slower walking speeds (Arpin et al., 2016). Others have similarly reported an association between force steadiness and performance on functional tests. For example, the time it takes healthy adults to complete a pegboard test of manual dexterity is positively correlated with the amplitude of force fluctuations during steady contractions (Marmon et al., 2011b), which suggests that the longer time it takes persons with MS to complete pegboard tests of dexterity may be related to declines in force steadiness (Hervault et al., 2017; Yozbatiran et al., 2006).

There were some similarities and some differences in the discharge characteristics of the three muscles examined in the current study compared with published data on healthy adults. Mean ISIs during steady isometric contractions (10 and 20% MVC force) for the MS participants were longest for soleus, shortest for tibialis anterior, and intermediate for gastrocnemius (Table 2). Similarly, mean ISIs in healthy subjects typically average 88 ± 18 ms for tibialis anterior during submaximal isometric contractions (Pasquet et al., 2005) and 131 ± 23 ms for soleus (Mochizuki et al., 2007) and ~90 ms for medial gastrocnemius (Vieira et al., 2012) during quiet standing. In contrast, the coefficient of variation for ISI during the
steady contractions in the current study was ~30% (Table 2), which is greater than nominal values for tibialis anterior (15.9 ± 9.61%; Jesunathadas et al., 2012), soleus (15.7 ± 4.7%; Mochizuki et al., 2007), vastus lateralis (~12%; Vila-Cha et al., 2010), and first dorsal interosseus (19.8 ± 2.5%; Moritz et al., 2005). Significantly, the coefficient of variation for the ISIs of the gastrocnemius motor units during the steady contraction at 10% MVC force was correlated with both measures of walking performance (Table 3), indicating a greater 6·min distance and faster 25·ft time were associated with more variable ISIs during the isometric contraction.

The measures of ISI distribution (skewness and kurtosis) in the current study (Table 2) were similar to those found for biceps brachii (skewness: 1.6 ± 0.6; kurtosis: 9.6 ± 7.3; Garland et al. 1994), but greater than those for first dorsal interosseus (skewness: 1.2 ± 0.6; kurtosis: 3.2 ± 2.9; Pascoe et al. 2014). These distributions indicated that there were a greater number of long ISIs than would be expected in a normal distribution (skewness = 0) and that more ISIs were clustered around the mean than expected in a normal distribution (kurtosis = 3). However, the ISI distributions for tibialis anterior had a greater number of long ISIs and were more clustered around the mean than those for gastrocnemius and soleus (Table 2).

The other regression analysis examined the associations between the clinical assessments and walking performance. The significant explanatory variables for the variance in both walking tests (6·min walk and 25·ft walk) were the PDDS score and time to complete the pegboard test of manual dexterity. The amount of variance explained by the two variables, however, was greater for the 6·min walk. The
correlations indicated that greater PDDS scores were associated with less distance walked in 6 min and longer times to walk 25 ft. This finding is consistent with previous reports of a significant association between PDDS score and 6-min distance (Learmonth et al., 2013; Sandroff et al., 2014; Socie et al., 2014). However, the stronger association between 6-min performance and PDDS scores rather than MSWS-12 scores was unexpected (Baert et al., 2014; Motl et al., 2010; Motl et al., 2013; Pilutti et al., 2013). Moreover, MSWS-12 scores have been reported to be correlated with 25-ft walk times (Baert et al., 2014; Hobart et al., 2013; Pilutti et al., 2013), yet did not emerge as an explanatory variable for the shorter walking test in the current study.

The other explanatory variable from the clinical assessments was the time to complete the grooved pegboard test. Tests of manual dexterity are more sensitive to changes in upper extremity function than other methods used to quantify disability in persons with MS (Feys et al., 2017; Goodkin et al., 1988; van Wissen et al., 2010; Yozbatirian et al., 2006). The current results, however, suggest that pegboard tests provide a systemic indication of disability status, consistent with prior reports of associations between manual dexterity and both activities of daily living (Paltamaa et al., 2007; Kierkegaard et al., 2012; Poole et al., 2010) and measures of walking performance (Drake et al., 2010; Kieseier et al., 2012).

In summary, moderate amounts of the variance in walking performance of persons disabled by MS were explained by selected neuromuscular characteristics of lower leg muscles and were associated with two other clinical assessments. The
neuromuscular characteristics comprised the mean discharge times of action potentials by motor units in plantar flexor muscles during steady submaximal contractions, the strength of the dorsiflexor muscles in the more affected leg, and force steadiness during a steady isometric contraction. The associated clinical assessments were a self-reported disability score and time to complete a pegboard test of manual dexterity. These findings indicate, for the first time, that the discharge characteristics of motor units innervating the plantar flexor muscles contribute significantly to differences in walking performance among individuals with MS.
CHAPTER V

NEUROMUSCULAR ELECTRICAL STIMULATION IMPROVES WALKING PERFORMANCE AND MUSCLE STRENGTH IN PEOPLE WITH MULTIPLE SCLEROSIS: DOUBLE-BLIND, RANDOMIZED TRIAL
ABSTRACT

Background: Multiple sclerosis (MS) eventually compromises the mobility of most individuals. Treatment with neuromuscular electrical stimulation (NMES) can restore some functional abilities in persons with MS, but its effectiveness may depend on stimulus-pulse duration.

Objective: To compare the effects of 6-wk intervention with narrow- or wide-pulse NMES on walking performance of persons with relapsing-remitting MS.

Methods: Individuals with MS (52.6 ± 7.4 yrs) were randomly assigned to either the narrow-pulse (n = 13) or wide-pulse (n = 14) group. The NMES intervention was performed on the dorsiflexor and plantar flexor muscles of both legs (10 min each muscle, 4-s on and 12-s off) at a tolerable level for 18 sessions across 6 wks. Outcomes were obtained before and after the intervention and 4 wks later.

Results: There was no influence of stimulus-pulse duration on the outcomes (P > 0.05), thus the data were collapsed across groups. The NMES intervention improved (P <0.05) walking performance, dorsiflexor strength in the affected limb, plantar flexor strength in the less affected limb, and fatigue.

Conclusion: A 6-wk intervention with NMES improved walking performance, strength of leg muscles, and fatigue in persons with relapsing-remitting MS. There was no influence of stimulus-pulse duration on the outcomes.
INTRODUCTION

Multiple sclerosis (MS) is a progressive neurological disorder that afflicts ~400,000 people in the US [MS Society website]. Although the course of the disease varies among individuals, it invariably involves the development of difficulties with walking, a decline in daily levels of physical activity, and a reduction in the quality of life (Heesen et al., 2008; Kos et al., 2008; Motl et al., 2011; Sutliff 2010). The adaptations in gait exhibited by individuals with MS are associated with declines in performance on both short- (25 ft, 10 m, and 30 m) and longer-distance (100 m, 2 min, and 6-min) walk tests (Kieseier & Pozzilli, 2012; Pilutti et al., 2013). The short-distance walk tests are used clinically to indicate walking disability, whereas the longer-distance walk tests provide a measure of walking endurance and functional capacity. Tests of walking endurance, such as the 6-min walk, are strongly associated with patient-reported measures of ambulation and fatigue (Gijbels et al., 2010; Motl et al., 2013; Savci et al., 2005).

The loss of mobility can be partially restored with exercise training (Sandroff et al., 2013; Snook & Motl, 2009), but primarily for persons with Expanded Disability Status Scale (EDSS) scores <4.0 (Motl & Pilutti, 2012). However, persons with greater levels of disability can experience some gains in physical function when exercise training is combined with neuromuscular electrical stimulation (NMES). For example, Broekmans et al. (2011) found similar gains in strength but no changes in clinical tests of mobility for individuals with MS (EDSS = 4.3 ± 02) who performed 20 wks of strength training exercises of the knee extensors either alone
or in combination with NMES. In contrast, Coote et al. (2015) reported that supplementing a 12-wk progressive resistance program with NMES augmented the gains in fatigue reduction, muscle endurance, and balance for individuals with MS who used a walking aid most of the time.

Conventional NMES protocols apply currents of <100 mA between electrodes placed on the skin over a target muscle at stimulus frequencies of 40 to 100 Hz with narrow pulse widths of 0.2 to 0.5 ms (Maffiuletti 2010). Recent work has shown that the capacity of NMES to influence the function of the nervous system depends on the duration of each stimulus pulse. Longer stimulus pulses (0.5 – 1.0 ms) — typically known as wide-pulse NMES—are able to produce more widespread responses in the nervous system than shorter stimulus pulses (0.2 – 0.4 ms) (Bergquist et al., 2012; Knash et al., 2003; Lagerquist et al., 2009; Mang et al., 2011) even after the stimulation has stopped (Mang et al., 2012; Stein et al., 2010).

The purpose of the study was to compare the effects of narrow- and wide-pulse NMES on the walking performance of persons with relapsing-remitting MS. Due to its greater engagement of sensory axons, wide-pulse NMES was expected to elicit more widespread adaptations in nervous system function and to produce greater gains in walking performance than conventional narrow-pulse NMES.

METHODS

The study enrolled 32 volunteers diagnosed with relapsing-remitting MS, self-reported difficulties with walking, and on stable doses of MS-related medications. Key exclusion criteria included history of seizure disorder, implanted biomedical
devices or metal, and skin disease. Five participants chose to leave the study due to time commitment or an unrelated injury. Twenty-seven persons (mean ± SD: 52.6 ± 7.4 yrs) completed the protocol. The Institutional Review Board at the University of Colorado Boulder approved the study protocol (# 13-0720).

In double-blinded, randomized design, participants were assigned to one of two groups: narrow-pulse group (n = 13; 54.9 ± 4.5 yrs) or wide-pulse group (n = 14; 50.4 ± 9.0 yrs). Each participant attended 3 evaluation sessions and 18 NMES treatment sessions distributed over 6 wks. Each evaluation session comprised 2 days of testing. Evaluation sessions were performed 1 wk before beginning the 6-wk treatment, within 1 wk after finishing the treatment (after), and approximately 4 wks (retention) after completing the treatment.

On the first day of the evaluation sessions, participants performed walking tests (25-ft walk test and 6-min walk test), a manual dexterity test (grooved pegboard), and completed three health-related questionnaires. Maximal walking speed was measured as the time it took to walk 25 ft as quickly as possible. The average of two trials was used as the measure of maximal walking speed. Walking endurance was characterized as the distance walked in 6-min around a 160-m track. Participants were encouraged to walk briskly, and the distance covered at 1-, 2-, 4-, and 6-min was recorded. Manual dexterity was quantified as the time taken to complete the grooved pegboard test, which required participants to place 25 pegs into holes on a pegboard as quickly as possible. The health-related questionnaires were the Patient
Determined Disease Steps (PDDS), Modified Fatigue Impact Scale (MFIS), and MS Walking Scale-12 (MSWS-12).

On the second day of the evaluation sessions, muscle strength and force steadiness were measured. Muscle strength was quantified as the peak torque (N\cdot m) achieved by the dorsiflexor and plantar flexor muscles of each leg while participants gradually increased muscle torque up to maximum and sustained it briefly. Participants performed 2-5 trials. When two maximal values were within 10% of each other, the greater value was designated as the maximal voluntary contraction (MVC) torque. Participants then performed submaximal isometric contractions with the dorsiflexor and plantar flexor muscles to match target forces of 10% and 20% MVC torque with the self-reported less affected leg. The task was to match the target force as closely as possible during two 30-s trials per target force and muscle group. Force steadiness was measured as the coefficient of variation for force.

Physical activity was measured with the GENEActive accelerometer (Activinsights Limited, Cambridge, UK) for 7 consecutive days beginning on the second day of evaluations. The monitor was worn on the same wrist at each evaluation with data collected at 30 Hz. Custom Matlab software (Matlab R2015a, Mathworks, Natick, MA) was used to filter (band pass of 0.2 to 15 Hz), calculate an average gravity-subtracted signal vector magnitude, quantify activity counts per second, and identify non-wear times (> 10 hrs). Maximum activity category cut-
points were set for Sedentary (1.35625), Light (4.03125), and Moderate (11.3125) accelerations per second.

The NMES treatments were applied with an FDA-approved clinical device (Vectra Genisys Therapy System) that delivered biphasic pulses of current through pairs of electrodes (2 x 3.5 in or 2 x 5 in each) placed on the skin overlying the muscles of each leg (Fig. 1). NMES was applied to the dorsiflexors and plantar flexors muscles (10 min each muscle, 4 s on and 12 s off) of each leg. NMES was applied to one leg at a time in a counterbalanced order across sessions. Stimulus frequency was set at 100 Hz with a pulse width of 1 ms for wide-pulse stimulation and at 50 Hz with a pulse of 0.26 ms for narrow-pulse stimulation. To reduce the discomfort associated with NMES, the participant was encouraged to contract the involved muscles while the stimulation was being applied.

The stimulation was applied while the participant was seated during the first and last two weeks (12 sessions) of the intervention and while standing in the middle two weeks (6 sessions). Current was progressively increased across sessions to the maximal tolerable level for each participant and then tapered during the last 3 sessions. After ~19 evoked contractions, the participant performed three passive stretching exercises with the involved leg muscles. The treatment sessions were performed or supervised by a physical therapist with clinical experience in providing such treatments. Each treatment session lasted ~50 min.
Figure 1. The intervention setup showing the stimulation pads locations over the plantar flexor (A) and dorsiflexor (D) muscles, the standing positions when stimulation was applied to the plantar flexor (B) and dorsiflexor (E) muscles, and the sitting position when stimulation was applied to the plantar flexor (B) and dorsiflexor (E) muscles.
Data analysis

The data were coded during analysis to maintain blinding. The Shapiro-Wilk test was used to assess normality. Normally distributed data were analyzed with mixed ANOVA and non-normally distributed data were analyzed with the Kruskal-Wallis test. Comparisons across time were examined with either one-way repeated-measures ANOVA (parametric) or Friedman’s test (non-parametric). When group differences reached significance, post-hoc comparisons were performed with either paired, independent t-tests (parametric data), Wilcoxon sign ranked, or Mann-Whitney U tests (non-parametric data).

Effect size for group differences were quantified as $\eta^2$ (parametric data) or as $\frac{z}{\sqrt{n_1 + n_2}}$ (non-parametric data). Effect sizes of 0.1 were considered small and those $\geq$ 0.5 were deemed large. Pearson and Spearman correlations were used to examine the associations between the outcomes and PDDS score. All statistical procedures were performed with SPSS (version 24.0; SPSS, Chicago, IL).

RESULTS

There were no significant differences between groups in the outcome measures obtained before the intervention (Table 1). The average scores for PDDS, MFIS, and MSWS-12 suggest that the participants were moderately disabled.
Table 1. Descriptive statistics for the two groups and combined group of participants prior to beginning the intervention.

<table>
<thead>
<tr>
<th></th>
<th>Wide (n= 14)</th>
<th>Narrow (n= 13)</th>
<th>Total (n= 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50.4 ± 9.0</td>
<td>54.9 ± 4.5</td>
<td>52.6 ± 7.4</td>
</tr>
<tr>
<td>PDDS</td>
<td>3.4 ± 1.3</td>
<td>3.6 ± 1.0</td>
<td>3.5 ± 1.2</td>
</tr>
<tr>
<td>MFIS score</td>
<td>42 ± 19</td>
<td>39 ± 21</td>
<td>41 ± 20</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>42 ± 12</td>
<td>45 ± 12</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>6-min walk (m)</td>
<td>410 ± 131</td>
<td>345 ± 138</td>
<td>379 ± 136</td>
</tr>
<tr>
<td>25-ft walk (s)</td>
<td>5.8 ± 2.1</td>
<td>11.9 ± 19.9</td>
<td>8.8 ± 13.9</td>
</tr>
<tr>
<td>Grooved pegboard test (s)</td>
<td>99 ± 35</td>
<td>107 ± 44</td>
<td>103 ± 39</td>
</tr>
<tr>
<td>Dorsiflexor torque (N•m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>11.4 ± 7.7</td>
<td>9.6 ± 5.9</td>
<td>10.5 ± 6.8</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>15.2 ± 6.4</td>
<td>14.5 ± 6.8</td>
<td>14.9 ± 6.5</td>
</tr>
<tr>
<td>Plantar flexor torque (N•m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>24 ± 14</td>
<td>22 ± 11</td>
<td>23 ± 12</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>26 ± 13</td>
<td>24 ± 9</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Dorsiflexor steadiness (% MVC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>6.3 ± 5.3</td>
<td>7.5 ± 5.2</td>
<td>6.9 ± 5.1</td>
</tr>
<tr>
<td>20%</td>
<td>4.8 ± 3.6</td>
<td>7.1 ± 6.4</td>
<td>5.9 ± 5.1</td>
</tr>
<tr>
<td>Plantar flexor steadiness (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>3.9 ± 3.1</td>
<td>3.6 ± 1.9</td>
<td>3.8 ± 2.5</td>
</tr>
<tr>
<td>20%</td>
<td>2.8 ± 1.5</td>
<td>3.7 ± 2.1</td>
<td>3.2 ± 1.8</td>
</tr>
</tbody>
</table>

No significant differences between groups.

There was no difference (Kruskal-Wallis test) between the two groups (wide- and narrow-pulse NMES) in the gains in 6-min walk distance (Chi-square = 0.25, df = 3, $P = 0.94$) or 25-ft walk speed (Chi-square = 4.85, df = 3, $P$ value = 0.18). However, both groups exhibited an effect of time (before, after, and retention) that was quantified by combining the data for the two groups.
Table 2. Health-related questionnaires, walking performance tests, and daily activities at the three time points during the 6-wk intervention (before, after, and retention).

<table>
<thead>
<tr>
<th></th>
<th><strong>Before</strong></th>
<th><strong>After</strong></th>
<th><strong>Retention</strong></th>
<th><strong>P value [effect size]</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PDDS</td>
<td>3.5 ± 1.2</td>
<td>3.1 ± 1.4</td>
<td>3.2 ± 1.5</td>
<td>0.19, [0.066]</td>
</tr>
<tr>
<td>MFIS score</td>
<td>41 ± 20</td>
<td>29 ± 16*</td>
<td>31 ± 16*</td>
<td>0.004 [0.212]*</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>43 ± 11</td>
<td>35 ± 13*</td>
<td>38 ± 13*</td>
<td>0.001 [0.33]*</td>
</tr>
<tr>
<td>6-min walk (m)</td>
<td>379 ± 136</td>
<td>415 ± 154*</td>
<td>421 ± 160*</td>
<td>0.001 [0.290]*</td>
</tr>
<tr>
<td>25-ft walk (s)</td>
<td>8.8 ± 13.9</td>
<td>7.9 ± 11.1 [0.304]*</td>
<td>7.8 ± 11.9 [0.43]*</td>
<td>0.003*</td>
</tr>
<tr>
<td>Grooved pegboard test (s)</td>
<td>103 ± 39</td>
<td>97 ± 34 [0.24]</td>
<td>93 ± 33 [0.24]</td>
<td>0.006*</td>
</tr>
<tr>
<td>Daily activity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>77.9 ± 6.6</td>
<td>76.5 ± 5.2</td>
<td>78.4 ± 6.1</td>
<td>0.171 [0.116]</td>
</tr>
<tr>
<td>Light</td>
<td>15.4 ± 4.6</td>
<td>15.8 ± 3.9</td>
<td>15.1 ± 4.3</td>
<td>0.546 [0.038]</td>
</tr>
<tr>
<td>Moderate-Vigorous</td>
<td>7.2 ± 3.1</td>
<td>8.5 ± 4.2</td>
<td>7.3 ± 3.4</td>
<td>0.059 [0.19]</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *P < 0.05 relative to before.
The relative (%) improvement in the distance walked in 6-min and time taken to walk 25 ft immediately after the intervention and 4 wks later (retention).

*Walking performance*

**6-min walk.** One-way repeated measures ANOVA with Bonferroni adjustment indicated significant improvements (*P* value [effect size]: 0.001 [0.29]) in the 6-min walk distance (Table 2). The increase (mean ± SD) in the distance walked in 6-min relative to before the intervention was 37 ± 51 m (12 ± 21%) after the intervention and 43 ± 66 m (13 ± 21%) at retention (Fig. 2).

**25-ft walk.** Friedman’s test with Wilcoxon sign ranked test for post-hoc comparison and adjusted *P* value indicated significant improvements in the 25-ft walk test after (7.9 ± 11.1 s [0.304]) and at retention (7.8 ± 11.9 s [0.43]) compared with before the intervention (8.8 ± 13.9 s) (Table 2). The decrease in time it took to walk 25 ft relative to before the intervention was −0.90 ± 3.1 s (5.1 ± 16.1%) after the intervention and −1.0 ± 2.3 s (8.1 ± 14.6%) at retention (Fig. 2).
There were no statistically significant differences between the gains in 6-min distance or 25-ft time measured after the intervention compared with those at retention whether the improvements were examined as either absolute (6-min: $P=0.27 \pm 0.14$; 25-ft: $P=0.33 \pm 0.13$) or relative (6-min: $P=0.5 \pm 0.09$; 25-ft: $P=0.23 \pm 0.16$) changes.

**Grooved pegboard test**

Friedman’s test with Wilcoxon sign ranked test for post-hoc comparison indicated significant differences ($P=0.006$) within the three groups, but the post-hoc test with adjusted $P$ value did not identify significant differences ($P=0.07$) between before ($103 \pm 39$ s) and either after ($97 \pm 34$ s [0.24]) or at retention ($93 \pm 33$ s [0.24]) (Table 2).
Table 3. Strength for muscles in affected and less affected legs and force steadiness for the less affected leg at the three time points during the 6-wk intervention (before, after, and retention).

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Retention</th>
<th>$P$ value [effect size]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dorsiflexor torque (N⋅m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>10.5 ± 6.8</td>
<td>12.7 ± 7.4 [0.29]*</td>
<td>13.5 ± 7.8 [0.38]*</td>
<td>0.016*</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>14.9 ± 6.5†</td>
<td>14.8 ± 6.5†</td>
<td>16.3 ± 10.0†</td>
<td>0.48 [0.03]</td>
</tr>
<tr>
<td><strong>Plantar flexor torque (N⋅m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected leg</td>
<td>22.6 ± 12.3</td>
<td>24.9 ± 11.6</td>
<td>25.8 ± 11.9</td>
<td>0.357 [0.04]</td>
</tr>
<tr>
<td>Less affected leg</td>
<td>25.0 ± 10.9</td>
<td>33.3 ± 18.8 [0.34]*†</td>
<td>28.3 ± 10.4 [0.25]</td>
<td>0.038*</td>
</tr>
<tr>
<td><strong>Dorsiflexor steadiness (% MVC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>6.9 ± 5.1</td>
<td>7.2 ± 6.2</td>
<td>6.3 ± 4.9</td>
<td>0.387</td>
</tr>
<tr>
<td>20%</td>
<td>5.9 ± 5.1¥</td>
<td>4.6 ± 4.0¥</td>
<td>5.3 ± 4.0</td>
<td>0.212</td>
</tr>
<tr>
<td><strong>Plantar flexor steadiness (% MVC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>3.8 ± 2.5‡</td>
<td>4.0 ± 2.6‡</td>
<td>3.3 ± 2.4‡</td>
<td>0.165</td>
</tr>
<tr>
<td>20%</td>
<td>3.2 ± 1.8‡</td>
<td>2.3 ± 1.1 *¥‡</td>
<td>2.4 ± 1.5*‡</td>
<td>0.005 [0.25]*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *$P$ < 0.05 relative to before. †$P$ < 0.05 relative to affected side. ‡$P$ < 0.05 relative to dorsiflexion. ¥ $P$ < 0.05 relative to 10% MVC.
Leg muscle function

Muscle strength. MVC torque (N·m) increased for two of the four tested muscle groups. The strength of the dorsiflexors in the affected leg increased ($P = 0.016$) after the intervention ($12.7 \pm 7.4$ N·m [0.29]) and at retention ($13.5 \pm 7.8$ N·m [0.38]) compared with before the intervention ($10.5 \pm 6.8$ N·m) (Table 3). The increase in dorsiflexor strength relative to before the intervention was $66 \pm 167\%$ after the intervention and $71 \pm 148\%$ at retention. Similarly, the strength of the plantar flexors in the less affected leg increased ($P = 0.038$) after the intervention ($33.3 \pm 18.8$ N·m [0.34]), but not at retention ($28.3 \pm 10.4$ N·m [0.25], $P = 0.064$), compared with before the intervention ($25.0 \pm 10.9$ N·m) (Table 3). The increase in plantar flexor strength relative to before the intervention was $39 \pm 54\%$ after the intervention and $26 \pm 58\%$ at retention. There were no statistically significant changes in the dorsiflexor torque of the less affected leg ($P = 0.48$ [0.03]) or the plantar flexors of the affected leg ($P = 0.36$ [0.04]).

These selective changes in muscle strength influenced the between-limb differences in muscle strength. Although the dorsiflexor muscles in the affected leg were stronger after intervention, they remained weaker than those in the less affected leg before ($P = 0.003$ [0.31]), after ($P = 0.048$ [0.15]), and at retention ($P = 0.045$ [0.16]) (Table 3). In contrast, it was the plantar flexor muscles in the less affected leg that gained strength during intervention, which made them even stronger than those in the affected leg ($P = 0.001$ [0.47]) (Table 3).
Force steadiness. The coefficient of variation for force during the steady isometric contractions (force steadiness) differed with target force (10% and 20% MVC), muscle group in the less affected leg (dorsiflexors and plantar flexors), and after the intervention. Force was more steady (lower coefficients of variation values) for the dorsiflexor muscles at 20% than at 10% MVC both before ($P = 0.039 \ [0.32]$) and after ($P = 0.003 \ [0.46]$) the intervention, but not at retention ($P = 0.18 \ [0.21]$) (Table 3). Plantar flexors were steadier at 20% than at 10% MVC, but only after the intervention ($P = 0.004 \ [0.44]$) and not before ($P = 0.31 \ [0.16]$) or at retention ($P = 0.058, \ [0.29]$) (Table 3). The plantar flexors were steadier than the dorsiflexors across all time points and at both target forces: 10% MVC, before ($P < 0.001 \ [0.53]$), after ($P = 0.021 \ [0.36]$), and retention ($P < 0.001[0.52]$); 20% MVC, before ($P = 0.008 \ [0.41]$), after ($P < 0.001 \ [0.58]$), and retention ($P < 0.001[0.57]$). Force steadiness improved ($P = 0.005 \ [0.25]$) for the plantar flexors at 20% MVC, but not at 10% MVC, after the intervention ($2.3 \pm 1.1\%$) and at retention ($2.4 \pm 1.5\%$) compared with before the intervention ($3.2 \pm 1.8\%$). There were no statistically significant changes in force steadiness for the dorsiflexors.

Daily levels of physical activity

There were no statistically significant changes in the daily levels of physical activity after the intervention or at retention in any of the three categories of physical activity: sedentary ($P = 0.17 \ [0.12]$), light ($P = 0.55 \ [0.04]$), and moderate-vigorous ($P = 0.06 \ [0.19]$) (Table 2).

Health-related questionnaires
MFIS ($P = 0.004 [0.212]$) and MSWS-12 ($P = 0.001 [0.33]$) scores were improved after the intervention and at retention, but the change in PDDS score after the intervention was not statistically significant ($P = 0.19 [0.066]$) (Table 2). However, there was a statistically significant correlation ($P < 0.05$) between PDDS score and the increase in distance (m) walked in 6-min after the intervention ($r = -0.40$): participants with greater PDDS scores experienced lesser gains in 6-min distance.

**DISCUSSION**

In a double-blind, randomized comparison of narrow- and wide-pulse NMES, individuals whose mobility was moderately impaired by MS showed clinically significant improvements in walking endurance and maximal walking speed due to the 6-wk NMES intervention. In contrast to the hypothesis, however, there was no influence of stimulus-pulse duration on outcomes.

These findings are similar to those of Coote et al. (2015), who found that supplementing a home-based resistance program with NMES applied to the knee extensor muscles of individuals who were moderately disabled by MS augmented the gains in muscle endurance and self-reported level of fatigue (MFIS). In contrast, the current study found that the NMES intervention, by itself, improved walking endurance, walking speed, fatigue, and self-reported levels of walking disability (MSWS-12 score). The improvements in 6-min walk test ($379 \pm 136$ m to $415 \pm 154$ m) and in the 25-ft walk test ($8.8 \pm 13.9$ s to $7.9 \pm 11.1$ s) represent clinically significant improvement in walking endurance (Armutlu et al., 2003) and the decrease in time to walk 25 ft ($8.8 \pm 13.9$ s to $7.9 \pm 11.1$ s) corresponds to a clinically
significant increase in maximal walking speed (Goldman et al., 2013). The gains in walking performance varied across participants and were inversely related to PDDS scores.

The current results provide some insight on adaptations that likely contributed to the improvements in walking performance. In a two-year longitudinal study, Zackowski et al. (2015) reported that the decrease in strength of the ankle dorsiflexor muscles (3.3 lbs/yr) for persons with MS was associated with an increase in the time it took to walk 25 ft; time changed by 0.19 s for each 1 lb decline in strength. We found that 18 sessions of NMES applied to the dorsiflexor and plantar flexor muscles of both legs increased the strength of the dorsiflexor muscles in the affected leg and elicited a transient increase in strength of the plantar flexors in the less affected leg. Given the critical role of the dorsiflexor muscles in limiting walking performance in persons with neurological disorders (Stein et al., 2010; Taylor et al., 2016), it seems likely that at least some of the improvements in walking endurance and maximal walking speed in the current study can be attributed to the increase in strength of the dorsiflexor muscles of the affected leg.

In addition to measuring the strength of the dorsiflexor and plantar flexor muscles, we examined an index of the neural drive to these muscles in the more affected leg during steady submaximal contractions. In this task, participants matched a target force displayed on a monitor as steadily as possible for 20 s. Quantification of the fluctuations in force during steady contractions (force steadiness) provides an index of the neural drive to muscle (Farina & Negro, 2015).
that is strongly correlated with other measures of motor function (Almuklass et al., 2016a; Chen et al., 2014; Kwon et al., 2014; Lodha et al., 2016; Marmon et al., 2011b). Moreover, physical training can improve force steadiness for individuals with essential tremor (Bilodeau et al., 2000) and for healthy old adults (Kornatz et al., 2005; Laidlaw et al., 1999).

Consistent with previous reports in which force steadiness is usually worse in weaker muscles (Tracy 2007; Tracy et al., 2007), the fluctuations in force during submaximal isometric contractions with the dorsiflexors were greater in the current study than those for the plantar flexors at both target forces. Compared with healthy individuals (Justice et al., 2014), however, the force fluctuations (coefficient of variation for force) for the dorsiflexors in the current study (5.9 ± 5.1 %) were greater than those for both young (1.20 ± 0.62 %) and older adults (1.74 ± 0.69 %). Similarly, force steadiness for the plantar flexors was greater for individuals with MS (3.8 ± 2.5 % at 10% MVC and 3.2 ± 1.8% at 20% MVC) than those for healthy adults (mean ± SE at 10% MVC force = 1.99 ± 0.16%) (Tracy 2007). These comparisons indicate that the neural drive to the dorsiflexor and plantar flexor muscles during submaximal isometric contractions is more variable for individuals with MS relative to healthy adults. Moreover, force steadiness for the plantar flexors at 20% MVC, but not the dorsiflexors, improved after the NMES intervention, which suggests an adaptation in the neural drive to these muscles that likely has consequences for motor function.
In conclusion, the 6-wk NMES intervention elicited clinically significant improvements in walking endurance and maximal walking speed in individuals whose mobility was moderately compromised by MS. In contrast to expectations, there was no influence of NMES stimulus-pulse duration on the outcomes. Secondary outcomes suggest that the improvements in mobility likely involve increases in muscle strength and the control of muscle force for some of the involved muscles, but the relative significance of these adaptations needs to be examined more systematically.
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