THESIS

RELATIONSHIPS AMONG NEUROPHYSIOLOGICAL, MOTOR PERFORMANCE, AND ATTRIBUTE DATA IN CHRONIC STROKE

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ABSTRACT

RELATIONSHIPS AMONG NEUROPHYSIOLOGICAL, MOTOR PERFORMANCE,

AND ATTRIBUTE DATA IN CHRONIC STROKE

The purpose of this descriptive study is to describe the relationships among neurophysiological, motor performance, and attribute data in individuals in chronic stages of stroke. Data obtained from 37 individuals who participated in previous research studies were analyzed. Results indicate significant relationships among neurophysiological measures of motor threshold, motor-evoked potential, intracortical facilitation, and intracortical inhibition, but these measures did not significantly relate to any motor performance or attribute data. Significant relationships were observed within motor performance data and between motor performance and attribute data, with the attribute of severity of the motor deficit having the most relationships. This study suggests that certain commonly used neurophysiological measures are unrelated to motor performance and attribute data.

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"I can do all things through Christ who strengthens me"

Philippians 4:13

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DEDICATION

I dedicate this work to my family. Thank you for your love and devotion to me. I love you all with my whole heart, forever.

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INTRODUCTION

Stroke Impairments are a Neurophysiological and Motor Problem

Stroke is a leading cause of long-term disability in the United States (CDC, 2015). Each year, over 795,000 people in the United States have a stroke (CDC, 2015). Among the many impacts stroke has on an individual, two prominent effects include neural damage within the brain and motor impairment (Pollock et al., 2014). Concerning neural damage, stroke cuts off blood flow to areas of the brain, resulting in neuron death and subsequent changes in neurological structure and functioning (Orchanian & Jamison, 2012). When such damage occurs within areas of the brain connected to movement, such as the sensory motor cortex, subcortical areas, and/or the cerebellum, motor impairment can occur (Pollock et al., 2014). One of the most disabling is hemiparesis of the upper limb contralateral to the brain lesion location, accompanied by reduced voluntary control, weakness, abnormal movement synergies, and stereotypical movements (Byl et al., 2003). Such impairments limit motor performance and interfere with the ability to engage in daily activities (Pollock et al., 2014).

Neuroplasticity and the Connection to Motor Performance Post-Stroke

Further examining stroke at the neurophysiological level reveals a very important concept for stroke recovery—neuroplasticity. Neuroplasticity refers to the ability of nerve cells to change their established nervous system in response to stimuli (whatisneuroplasticity.com, 2011). Such stimuli include responses to development, the environment or disease (such as stroke), learning, or therapy, and the results can have both adaptive as well as maladaptive effects on motor performance (Cramer et al., 2011). In stroke, maladaptive neuroplasticity can

cause neuronal structures associated with a lesion or area of the brain damaged by a stroke to decrease blood supply and metabolism (McCormack, 2009). Such maladaptive neuroplasticity can lead to loss of voluntary production of movement and motor control as seen within hemiparesis post-stroke (Pollock et al., 2014). On the other hand, adaptive neuroplastic changes post-stroke can cause dendritic growth and the growth of new blood vessels near areas damaged by stroke, which can contribute to improved motor control post-stroke (Arya et al., 2011; McCormack, 2009).

Several research studies highlight the difference between adaptive and maladaptive neuroplasticity post-stroke. Research by Krakauer (2006) showed maladaptive neuroplastic changes in the primary motor cortex post-stroke leading to hand weakness and subsequent compensatory shoulder and elbow movement during reaching (as cited in Jang, 2013). Likewise, research by Schwerin et al. (2008) showed that increased excitability in the affected motor pathway post-stroke was associated with abnormal extension synergy in the affected arm (as cited in Jang, 2013). Conversely, research by Gauthier et al. (2008) showed adaptive neuroplastic changes post-stroke (likely induced by intensive and concentrated receptive practice of motor skills) leading to increases in gray matter in sensory and motor areas of the brain after constraint-induced movement therapy (CIMT), correlating with improved motor performance in the affected upper extremity. Studies by Lacourse et al. (2004) and Page et al. (2009) also showed adaptive neuroplastic changes post-stroke including increased activation in premotor, primary cortex, cerebellar, and striatal sensorimotor networks after mental practice, correlating with improved motor performance in the affected upper extremity (as cited in Arya et al., 2011). Clearly, cortical neuroplastic changes have an effect on motor stroke recovery.

Cortical Excitability and Inhibition as a Measure of Neuroplasticity

The current study looks specifically at measures of cortical excitability and inhibition typically associated with neuroplastic changes. The basic neurophysiologic unit of interest is the excitable neuron whose action potential causes the release of neurotransmitters into synapses, which can either depolarize the membrane of the postsynaptic neuron, bringing it closer to an excitatory threshold, or hyperpolarize the membrane and create an inhibitory effect (Tortora & Derrickson, 2009). Therefore, cortical neurons can be either excitatory and increase the amount of descending motor output, or inhibitory and reduce descending motor output in the brain (Hallett, 2007).

Transcranial Magnetic Stimulation as a Method to Detect Neuroplastic Changes

Such cortical excitability- and inhibition can be detected through a technique called transcranial magnetic stimulation (TMS). TMS is a technique in which an electrical current is produced within a heavily insulated coil of wire. This sets up a magnetic field between the stimulator and the skull perpendicular to the electrical field, which then penetrates the skull into the brain and induces another electrical field within the cortical neurons (George & Belmaker, 2007; Hallett, 2007). The thought is that this induced electrical field activates cortical interneurons within the cerebral cortex (Perocheau, Laroche, & Perrot, 2014), resulting in altered cortical activity (Tortora & Derrickson, 2009). This cortical activity can be examined by neurophysiological measures of motor-evoked potential, motor threshold, intracortical facilitation, and intracortical inhibition, which are each explored in the current study.

TMS Measurements of Cortical Activity and Their Relationships with Each Other

Motor-evoked potential (MEP) and motor threshold. Motor-evoked potential (MEP) and motor threshold (MT) are perhaps the two most commonly used TMS measures. MEP is a muscle twitch (evoked usually by primary motor cortex TMS) typically measured via surface electromyography (EMG). It is a global measure of corticospinal excitability (George & Belmaker, 2007). Single-pulse MEP amplitude is measured peak to peak on the EMG wave and typically increases with increased stimulation intensity (George & Belmaker, 2007). In individuals post-stroke, single-pulse MEP amplitude is typically shown to be smaller as compared to individuals without stroke (Brouwer & Schryburt-Brown, 2006; Cortes, Black-Schaffer, & Edwards, 2012; Malcolm, Vaughn, & Greene, 2014).

According to Rossini et al. (1999), MT is the minimum TMS intensity required to produce a MEP (a small MEP is considered to be greater than 50 microvolts) in at least half of the stimulus trials (as cited in George & Belmaker, 2007). In individuals post-stroke, MT is typically shown to be higher as compared to individuals without stroke (Brouwer & Schryburt-Brown, 2006; Cortes et al., 2012; Hosomi et al., 2013; Malcolm et al., 2014), and has been shown to be higher in the ipsilesional as compared to the contralesional hemisphere (Brouwer & Schryburt-Brown, 2006; Liepert, 2006). In general, MT and single-pulse MEP amplitude are inversely related: Individuals demonstrating higher MT also exhibit lower single-pulse MEP amplitude (Liepert, 2006). While MT and single-pulse MEP are commonly used measures of corticospinal excitability, two other measures yield more precise information about intracortical excitability. These measures are intracortical facilitation and intracortical inhibition, discussed next.

Intracortical Facilitation and Inhibition. Using a TMS stimulus below the threshold (sub-threshold) for creating an MEP paired with a subsequent stimulus strong enough to create an MEP (supra-threshold) can modify MEP amplitudes (Liepert, 2006). When these two stimuli (i.e., paired-pulse stimuli) are delivered in longer intervals (15 ms), they cause the MEP amplitude to be enlarged, i.e., the paired stimuli *facilitate* larger amplitude MEPs. This is a process called intracortical facilitation (Liepert, 2006). Intracortical facilitation (ICF) reflects excitability of N-Methyl-D-aspartic acid (NMDA) receptor-dependent excitatory interneuronal circuits in the motor cortex (George & Belmaker, 2007). It is a net facilitation consisting of stronger facilitation and weaker inhibition. When long-interval paired-pulse stimuli are administered in the presence of an NMDA antagonist, ICF decreases (George & Belmaker, 2007). In individuals in chronic stages of stroke, ICF in the affected hemisphere has been shown to be less (smaller MEP amplitudes) than in individuals without stroke (Edwards et al., 2013; Malcolm et al., 2014).

When the sub-threshold and supra-threshold TMS stimuli are delivered in shorter intervals (2 ms) in the healthy brain, they cause the MEP amplitude to be suppressed. This process is called intracortical inhibition (Liepert, 2006). Intracortical inhibition (ICI) is net inhibition consisting of stronger inhibition and weaker facilitation. Increase in gamma-aminobutyric acid (GABA) neurotransmission results in ICI (George & Belmaker, 2007), or a prevailing inhibitive influence. In individuals in chronic stages of stroke, ICI in the affected hemisphere has been shown to be less (less inhibition, therefore larger MEP amplitudes) than in individuals without stroke (Liepert, 2006; Malcolm et al., 2014).

Both ICF and ICI are measures of intracortical excitability within the primary motor cortex (Liepert, 2006). Since the subthreshold stimulus (first stimulus in the paired-pulse) used to

measure ICF and ICI are too weak to create an MEP (George & Belmaker, 2007), ICF and ICI are considered to be purely cortical measures and thus, are more precise measures of intracortical excitability (Chen, 2004).

Limited research exists to assess the relationships between ICI and ICF and between affected-hemisphere MT and single-pulse MEP amplitude compared to affected-hemisphere ICI and ICF in chronic stroke. However, in a descriptive study of 24 participants in chronic stages of stroke, Honaga et al. (2013) observed that affected-hemisphere ICI did not correlate with single-pulse MEP amplitude, suggesting that ICI does not relate to corticospinal excitability, rather, it relates to altered inhibitory activity within the brain.

Because there is limited research assessing the relationships between affected-hemisphere MT and single-pulse MEP amplitude compared to affected-hemisphere ICI and ICF in chronic stroke, the current study will examine those relationships.[1]

Relationships among Motor Performance Measures

The current study explores the motor performance measures of the affected upper extremity using the Fugl-Meyer (FM) Assessment, Motor Activity Log (MAL), and grip strength obtained by a dynamometer. The FM is an evaluative measure of sensorimotor recovery in hemiplegic stroke (Gladstone, Danells, & Black, 2002), often used exclusively for examining motor recovery in the hemiparetic arm. The MAL is a self-report measure of actual use of the hemiparetic arm for daily functional tasks outside of the laboratory setting (Uswatte et al., 2006). For more detailed descriptions of these measures, please see the Method section of this paper.

[1] Because the intracortical effects of both ICI and ICF are measured by recording MEP amplitude, for clarity, single-pulse MEP amplitude will be referred to as "MEP amplitude," and ICI and ICF MEP amplitudes will simply be referred to as "ICI" and "ICF" throughout this paper.

Research supports relationships between the FM, MAL, and grip strength measures. In a descriptive study of 93 participants in chronic stages of stroke, Harris and Eng (2007) found a significant and moderately strong positive Spearman correlation (r=.61, p<.01) between grip strength scores and MAL scores of the affected upper extremity. In a sample of 14 participants in chronic stages of stroke who had participated in CIMT, Takebayashi et al. (2015) found a significant and excellent-strength positive correlation between FM scores and scores on the Amount of Use scale of the MAL of the affected upper extremity (r=.778, p=.001). Though the relationship was not explicitly stated, in a sample of 10 participants in chronic stages of stroke, Cha, Ji, Kim, & Chang (2014) observed that both grip strength scores and FM upper extremity scores of the affected upper extremity significantly improved after transcranial direct current stimulation (a method of brain stimulation similar to TMS).

The current study adds to the descriptive research of the relationship between grip strength and MAL scores of the affected upper extremity, specifically with MAL scores relating to participant-perceived quality of movement. As most relationships between MAL and FM, and FM and grip strength reported in the research have so far been obtained after therapy, the current study will address any relationships observed unconditioned by therapy.

Relationships between Neurophysiological Measures and Motor Performance Measures

The current study explores the relationship between neurophysiological measures of MT, MEP, ICF, and ICI and motor performance measures including the FM, MAL, and grip strength.

MT, MEP, and motor performance. Research suggests that lower MT and larger MEP amplitudes correlate with better motor performance in the stroke affected upper extremity. In a descriptive study of 14 individuals in chronic stages of stroke, Brouwer and Schryburt-Brown

(2006) showed that lower MT and larger MEP amplitudes were related to better motor performance of the affected hand, measured by assessments of a keyboard tapping task, Purdue pegboard task, and first digital interosseous muscle (FDI) strength task. Likewise, in a study of 10 participants post stroke, nine of whom were in chronic stages, Koski, Mernar, and Dobkin (2004) found that a decrease in MT in the affected hemisphere correlated with improvements in motor performance of the affected upper extremity as measured by the Wolf Motor Function Test (WMFT) and FM upper extremity scale after occupational therapy.

Moreover, in a sample of 12 participants in chronic stages post-stroke, Liepert (2006) found a tendency for MEP amplitudes to be increased after CIMT. This increase in MEP amplitude was negatively related to MT, which decreased after CIMT. Hence, the motor cortex became more excitable after CIMT. While any significant relationships between MT, MEP amplitude, and motor function were not reported, Liepert (2006) reported that all participants in the study had improved motor performance of the affected upper extremity as measured by the WMFT and MAL.

As much of the literature linking neurophysiological and motor performance data examines relationships observed after some sort of therapeutic intervention, the current study examines relationships between neurophysiological and motor performance data unconditioned by therapy. Additionally, and perhaps more importantly, no literature to date has reported the relationships between such a large number of variables, which when studied together, provide a more comprehensive and detailed picture of how neurophysiological measures relate to each other and motor performance measures.

ICI, ICF, and motor performance. Conflicting and limited research exists concerning the relationship between affected-hemisphere ICI, ICF, and affected-upper extremity motor performance in chronic stroke. In a sample of 30 participants in chronic stages of stroke who had participated in repeated muscle vibration and physiotherapy, Marconi et al. (2011) found that a higher level of ICI in the affected hemisphere was associated with higher functional scores of the affected upper extremity on the Motricity Index for the upper limbs and the WMFT., Furthermore, in a descriptive study of 24 participants in chronic stages of stroke, Honaga et al. (2013) found ICI in the affected hemisphere significantly and negatively correlated with motor performance of the affected upper extremity: participants with greater ICI (i.e., smaller MEP amplitudes during ICI testing) displayed higher scores on the Stroke Impairment Assessment Set (SIAS) finger function test and the FM upper extremity motor test. Conversely, in a sample of 12 participants in chronic stages of stroke who participated in CIMT, Liepert (2006) found no relationship between ICI in the affected hemisphere and motor performance measures of the affected upper extremity on the WMFT and the MAL: As compared to pre-test values, both greater and lesser ICI values were obtained after CIMT. Therefore, since all participants improved in motor performance after CIMT, Liepert (2006) concluded that both increases and decreases in ICI can be associated with improvements in motor function. Liepert (2006) also found no significant relationship between ICF in the affected hemisphere and motor performance of the affected upper extremity as measured by the MAL and WMFT.

Limited research exists connecting neurophysiological measures of the affected hemisphere to grip strength of the affected hand in the chronic stage of stroke. However, in a study of eight participants followed from the acute stage through the chronic stage of stroke

(one year post-stroke), Liuzzi et al. (2014) observed that more reduction in movement-related ICI in the affected hemisphere within the first week post-stroke was related to better motor performance of the affected hand as measured by grip strength and finger-tapping speed over one year. The current study expands this research into chronic stages of stroke and with additional measures of MT, MEP amplitude, and ICF. Such relationships have not been well understood in survivors in chronic stages of stroke, who may present differently than those in acute or sub-acute phases.

Relationships between Neurophysiological and Attribute Measures

The current study explores the attribute measures of lesion location (cortical or subcortical), hemisphere (left or right), chronicity (months since stroke), age, and stroke severity of the motor impairment (mild versus moderate-severe based on FM scores) and their relationship with affected-hemisphere neurophysiological measures, obtained through TMS. A review of the literature highlights what is known about these relationships.

Stroke lesion location and TMS measures. Conflicting evidence exists concerning the relationship between affected-hemisphere TMS measures and stroke lesion location in chronic stroke. In a sample of 30 participants in chronic stages of stroke who had participated in repeated muscle vibration and physiotherapy, Marconi et al. (2011) found that participants with a cortical lesion had lower MT in the affected hemisphere than those with subcortical lesions, suggesting that the site of the lesion determines cortical excitability. Conversely, in a descriptive study of 24 participants in chronic stages of stroke, Honaga et al. (2013) found MT of the affected hemisphere to be significantly higher in participants with cortical and subcortical strokes compared to seven healthy controls, but no significant difference in MT between

subcortical and cortical groups. Concerning MEP amplitude, Honaga et al. (2013) also found MEP amplitudes in the affected hemisphere to be significantly smaller in participants with both cortical and subcortical strokes as compared to seven healthy controls but did not report if there were any differences in MEP amplitude between cortical and subcortical groups. However, in a study of 12 participants in chronic stages of stroke, Liepert (2006) found no difference in MEP amplitude of the affected hemisphere between cortical and subcortical lesions.

There is certainly varying information about lesion location and cortical excitability. The current study adds to the existing research to explicate the relationship between lesion location and affected-hemisphere TMS measures.

Chronicity and TMS measures. Limited research exists connecting affected-hemisphere TMS measures in chronic stroke to chronicity. Regarding MT and ICI, in a descriptive study of 24 participants in chronic stages of stroke, Honaga et al. (2013) found no correlation between MT of the affected hemisphere and time from onset but did find that ICI of the affected hemisphere significantly and inversely correlated with the time from onset. The current study expands this research and includes exploration of relationships of chronicity including MEP amplitude and ICF.

Hemisphere and TMS measures. Existing research is also limited relating affected-hemisphere TMS measures in chronic stroke based on whether the stroke occurred in the left or right hemisphere. In one study of 30 participants in chronic stages of stroke who participated in repeated muscle vibration and physiotherapy, Marconi et al. (2011) found no relationships between TMS measures of MT, MEP, ICI, and ICF between strokes that occurred in the right or left hemisphere. The current study adds to this research.

Age and TMS measures. To the author's knowledge, no research exists examining the relationship between affected-hemisphere TMS measures in chronic stroke based on age. The current study may be the first to examine this relationship.

Stroke severity and TMS measures. To the author's knowledge, no research exists examining the relationship between affected-hemisphere TMS measures and FM scores in chronic stroke based on mild or moderate-severe motor impairments. The current study may be the first to examine this relationship. Neurophysiological measures are often used in research to examine neuroplastic changes post-stroke, and TMS administered in a repetitive manner is used to induce adaptive neuroplasticity to ameliorate the stroke-induced motor impairment. Therefore, understanding the severity of motor impairment in terms of TMS measures, can provide valuable information of what at the brain level may constitute better or worse motor impairment at the upper extremity level.

Relationships between Motor Performance Measures and Attribute Measures

Lesion location and motor function. Limited and conflicting research exists examining the relationship between stroke lesion location and motor performance of the affected upper extremity. In a study of 12 participants in chronic stages of stroke who participated in CIMT, Liepert (2006) found that participants with cortical and subcortical lesions improved in motor performance in the affected upper extremity to a similar extent as measured by the MAL and WMFT. Similarly, in a descriptive study of 72 participants in chronic stages of stroke, Honaga et al. (2013) found there to be no significant difference in motor performance in the affected upper extremity as assessed by the FM between participants who had cortical lesions and participants who had subcortical lesions. Conversely, in a study of 30 participants in chronic stages of stroke

who participated in repeated muscle vibration and physiotherapy, Marconi et al. (2011) observed that participants with cortical lesions had better motor performance outcomes in the affected upper extremity than participants with subcortical lesions, measured by the Motricity Index for the upper limbs and the WMFT. The current study further explores the connection between lesion location and motor performance of the affected upper extremity.

Hemisphere and motor performance. Research suggests the hemisphere of the lesion and motor performance of the affected upper extremity are not related. In a study of 30 participants in chronic stages of stroke who participated in repeated muscle vibration and physiotherapy, Marconi et al. (2011) found no relationships between the stroke-affected hemisphere (right or left) and motor performance as measured by Motricity Index for the upper limbs and the WMFT. Likewise, in a descriptive study of 93 participants in chronic stages of stroke, Harris and Eng (2006) found no significant difference in grip strength or MAL measures of the affected upper extremity between participants with right or left hemisphere lesions.

Chronicity and motor performance. As more research emerges supporting the notion that gains in motor performance can result even in chronic stages, examining the relationship between chronicity and motor performance is warranted. Research suggests chronicity and motor performance of the affected upper extremity in chronic stroke are not related. In a descriptive study of 72 participants in chronic stages of stroke, Honaga et al. (2013) found motor performance of the affected upper extremity scores of the SIAS finger function and FM upper extremity motor tests did not correlate with time from onset of stroke. Likewise, in a study of 43 participants in chronic stages of stroke who participated in CIMT, Gauthier et al. (2014) also

found no relationship between chronicity and motor function of the affected upper extremity as measured by WMFT and MAL Quality of Movement scale assessments.

Age and motor performance. Limited research exists detailing the relationship between age and motor performance of the affected upper extremity in chronic stroke. In a descriptive study of 50 participants in acute stages of stroke (ranging in age from 47 to 86 years), Ferrucci et al. (1993) showed that baseline FM scores for participants over 65 years old were lower than participants under 65 years old. Conversely, in a sample of 43 participants in chronic stages of stroke who participated in CIMT, Gauthier et al. (2014) found no significant differences in motor performance of the affected upper extremity as measured by the WMFT and the MAL based on age. However, these differences in findings may have been due to the method of analysis each study used. Ferrucci et al. (1993) split age into older and younger groups and Gauthier et al. (2014) kept age as parametric data. Additionally, Ferrucci et al. (1993) studied individuals in acute stages while Gauthier et al. (2014) studied individuals in chronic stages, which may have added to the differences in the findings. The current study expands the work of Ferrucci et al. (1993) by examining younger and older groups in the chronic stage of stroke.

Stroke severity based on motor impairment and motor performance. Research suggests that severity of the stroke-related motor impairment and motor performance are related in chronic stroke. In a descriptive study of 92 participants in chronic stages of stroke, Harris & Eng (2006) observed that compared to individuals with milder motor impairments, grip strength was significantly more impaired in individuals with more severe motor impairments (measured by FM scores), and MAL scores were significantly lower.

Purpose

Because most research of survivors in chronic stages of stroke have been after therapy, and because no literature to date has considered the relationships between this large number of variables, the purpose of this descriptive study is to contribute to current research regarding relationships of pre-therapy neurophysiological measures to each other and to motor performance and attribute measures. The current study will answer the following questions:

1. Are there significant relationships among pre-therapy neurophysiological measures (obtained by TMS), in individuals in chronic stages of stroke?
2. Are there significant relationships among pre-therapy motor performance measures (grip strength, FM, and MAL) in individuals in chronic stages of stroke?
3. Are there significant relationships between pre-therapy neurophysiological (obtained by TMS) and motor performance measures in individuals in chronic stages of stroke?
4. Are there significant relationships between pre-therapy neurophysiological (obtained by TMS) and attribute measures in chronic stages of stroke?
5. Are there significant relationships between pre-therapy motor performance and attribute measures in individuals in chronic stages of stroke?

METHOD

Participants

The current study is a retrospective study of data collected in two previously completed research trials. Participants in these studies all provided written informed consent and met the following inclusion criteria: Chronic stages (6 months or more after onset) of unilateral ischemic or hemorrhagic stroke, active extension of at least 20º at the stroke-affected wrist, active extension of at least 10º at the stroke-affected metacarpophalangeal and interphalangeal joints of at least two fingers and thumb, approximately 30º of active flexion in the stroke-affected shoulder, a score of 24 or above on the Mini Mental Status Exam, and the ability to actively participate for approximately two hours during experimental sessions. Consistent with safety guidelines of TMS (Anand & Hotson, 2002; Keel, Smith, & Wasserman, 2001; Rossi, Hallet, Rossini, Pascual-Leone, and the Safety of TMS Consensus Group, 2009), participants were excluded if they were taking medications that could lower the seizure threshold; had a history of seizures or epilepsy, mass brain lesions, epileptiform activity on an EEG, or heart disease; had a pacemaker, medication pump, metal plate within the skull, metal objects within the eye or skull, or intracardiac lines; were pregnant; or were under 21 years old. For the current study, pre-therapy data were analyzed from the 37 participants who completed the previous studies.

Materials

Fugl-Meyer Assessment. Motor performance measures of the stroke-affected arm were analyzed from data collected with the FM assessment. The FM is an evaluative instrument of sensorimotor recovery in hemiplegic stroke (Gladstone, Danells, & Black, 2002). For the current

study, upper extremity motor scores were analyzed, including items measuring movement and coordination of the stroke-affected shoulder, elbow, forearm, wrist, and hand. Scores can range from 0 (complete hemiplegia) to 60 (normal motor movement), excluding reflex measures.

The FM has excellent test-retest reliability (ICC = 0.97) for total motor score in a general rehabilitation population including stroke (Platz et al., 2005), excellent interrater reliability (*r*=0.995-0.996) for the upper extremity in a chronic stroke population (Duncan et al., 1983), and has a minimal detectable change of 5.2 points for the upper extremity portion of the assessment in a chronic stroke population (Wagner et al., 2008).

Motor Activity Log. Motor performance measures of the stroke-affected arm were also analyzed from data collected with the MAL. The MAL is a self-report instrument of actual use of the hemiparetic arm for daily functional tasks outside of the laboratory setting (Uswatte et al., 2006). The area assessed for this study was the Quality of Movement scale, ranging from 0 (not used) to 5 (normal), and averaged among the 30 possible activities that participants reported they did. The MAL Quality of Movement scale has high internal consistency (α=0.91) and excellent test-retest reliability (*r*=0.61 to 0.71) in a stroke population (Van der Lee et al., 2004).

Dynamometer. Grip strength of the stroke-affected hand was analyzed from data collected using a Sammons Preston, Inc. dynamometer, averaged among three trials one minute apart, in kilograms.

TMS instrument. MT, MEP amplitude, ICI, and ICF measures were analyzed from data collected using a Magstim Super Rapid magnetic stimulator and figure eight coil (Magstim, LTD, UK). All TMS measures were obtained from the stroke-affected hemisphere.

TMS procedures. Study procedures are outlined in Massie, Tracy, and Malcolm (2013). Briefly, participants were seated in a chair while receiving TMS. MT, MEP amplitude, ICI, and ICF measures were obtained through EMG recordings from the first dorsal interosseous (FDI) muscle of the stroke-affected hand. A pair of eight-millimeter surface electrodes were arranged in a belly-tendon pattern over the FDI muscle for obtaining EMG activity, and the EMG was recorded with a PowerLab 16/30 system. The Magstim coil was placed upon the head with the handle in a posterior position, inducing a posterior-to-anterior current. Stimulation was provided over the motor cortex area of the affected hemisphere that consistently produced the highest MEP amplitude in the stroke-affected FDI muscle.

MT (with FDI at rest) was determined by the value of the lowest intensity stimulation that elicited an MEP of at least 100 microvolts in half of the stimulus trials. ICI was measured by pairing the sub-threshold stimulus (90% of MT) and the supra-threshold stimulus (116% of MT) 2 milliseconds apart. ICF was measured by pairing the sub- and supra-threshold stimuli at the same intensities as ICI but 15 milliseconds apart. ICI, ICF, and MEP amplitude were obtained by randomly delivering 12 stimuli for each condition. Peak to peak amplitudes were measured for each MEP obtained through paired pulse (ICI and ICF) stimulation and single-pulse stimulation (MEP amplitude), and means and standard deviations were calculated. Any values beyond two standard deviations were excluded, and means were recalculated.

Data Analysis

Due to the nonparametric nature of the attribute data, stroke hemisphere, lesion location, and stroke severity of the motor deficit were split into groups for analysis. Stroke hemisphere was split into left and right. Lesion location was split into groups of cortical

(including strokes classified as both cortical only as well as cortical and subcortical) and all others that were not cortical, which included purely subcortical, brainstem, basal ganglia, and cerebellar. Stroke severity of the motor deficit was measured using FM cutoff scores, wherein 0-19 indicated severe, 19-47 indicated moderate, and 47+ indicated mild (Woodbury et al., 2013). Based on these cutoffs, stroke severity was dichotomized as mild versus moderate-severe. Also, though age is typically parametric data, due to the previously mentioned research demonstrating differences in baseline motor function based on age under or over 65 years (Ferrucci et al., 1993), age was split into groups of 21 years to 65 years versus 66 years and older.

Pearson correlations were run among MT, MEP, ICF, ICI, chronicity, FM, and grip strength measures since they were all interval/ratio data. Since MAL measures are ordinal in nature, Spearman correlations were run to explore associations between MAL and MT, MEP, ICF, ICI, chronicity, FM, and grip strength measures. For correlation strength, correlation coefficients above .75 were interpreted as good to excellent strength,.50 to .75 as moderate to good strength,.25 to .50 as fair strength, and 0.00 to .25 as no or a very weak relationship (Portney & Watkins, 2000). Multiple analysis of variance (MANOVA) were run to determine differences in MT, MEP, ICF, ICI, FM, and grip strength using age, stroke hemisphere, lesion location, age, and stroke severity as grouping variables. Kruskal-Wallis tests set at alpha level .05 were run to determine differences in ordinal MAL scores based on age, stroke hemisphere, lesion location, and stroke severity.

RESULTS

Participants

The 37 participants included 19 males, mean age of 66 years (*SD*=11.02 years), and 18 females, mean age of 58 years (*SD*=14.42 years). Twenty-one participants were in the age range of 21 years to 65 years, and 16 were 66 years or older. For the whole group, mean time since stroke was 3.31 years (*SD*=3.05 years). Seventeen participants had a left hemisphere stroke, 16 had a right hemisphere stroke, and 4 had a stroke hemisphere designated as "other," which were omitted from analysis. Twelve participants had a stroke with either cortical only or both cortical and subcortical involvement, 22 had a stroke with subcortical and no cortical involvement, and 3 had a stroke lesion location designated as "other," which were omitted from analysis. Twenty-three participants had a moderate-severe stroke, 13 had a mild stroke, and 1 participant did not have severity data available, so was omitted. (See Table 1.)

Relationships among Neurophysiological Data

As shown in Figure 1, significant and moderately strong negative correlations were observed between MT and MEP amplitude (r=-.534, p=.001), such that participants with higher MT displayed smaller MEP amplitude responses to single pulse TMS. Significant and fairly strong negative correlations were observed between MT and ICF (r=-.360, p=.003), such that participants with higher MT displayed less ICF (i.e., smaller MEP amplitudes obtained during ICF testing). Significant and fairly strong negative correlations were observed between MT and ICI (r=-.473, p=.007), such that participants who had higher MT displayed greater ICI (i.e., smaller MEP amplitudes obtained during ICI testing).

TABLE 1. Demographic Data for Study Participants

Participant	Age (In Years)	Chronicity (In Months)	Stroke Hemisphere	Lesion Location	Stroke Severity
Males (*n*=19)					
1	44	8	R	Cortical	moderate-severe
5	61	16	Other	Other	Mild
6	74	48	Other	Subcortical	moderate-severe
7	86	49	Other	Other	moderate-severe
8	63	166	L	Cortical	moderate-severe
9	68	19	L	Cortical	Mild
10	54	9	L	Subcortical	moderate-severe
14	51	72	L	Cortical	moderate-severe
16	70	56	L	Cortical	Mild
18	70	32	R	Subcortical	missing data
19	77	23	R	Other	Mild
20	63	15	L	Subcortical	moderate-severe
25	70	12	R	Subcortical	moderate-severe
26	82	22	R	Subcortical	moderate-severe
29	57	20	L	Cortical	mild
30	72	24	L	subcortical	moderate-severe
34	80	87	R	cortical	moderate-severe
36	53	12	L	subcortical	moderate-severe
37	60	9	Other	subcortical	mild
Mean	*66.1 yrs*	*36.8 mos*			
Standard Deviation	*11.3 yrs*	*38.6mos*			
Totals			*6 R*	*7 cortical*	*6 mild*
			9 L	*9 subcortical*	*12 moderate-severe*
			4 other	*3 other*	*1 missing data*
Females (*n*=18)					
2	42	36	L	cortical	moderate-severe
3	74	60	R	subcortical	moderate-severe
4	66	82	L	subcortical	mild
11	65	21	L	subcortical	mild
12	75	37	R	subcortical	mild
13	41	6	R	cortical	mild
15	63	36	R	subcortical	moderate-severe
17	64	44	L	subcortical	mild
21	21	145	L	subcortical	mild
22	56	65	R	subcortical	moderate-severe
23	51	12	R	subcortical	moderate-severe
24	66	80	R	subcortical	moderate-severe
27	71	38	R	subcortical	moderate-severe
28	40	12	L	cortical	moderate-severe
31	61	12	L	subcortical	moderate-severe
32	47	16	L	cortical	mild
33	61	9	R	subcortical	moderate-severe
35	77	59	R	cortical	moderate-severe
Mean	*57.8 yrs*	*42.8 mos*			
Standard Deviation	*15 yrs*	*35.2 mos*			
Totals			*10 R*	*5 cortical*	*7 mild*
			8 L	*13 subcortical*	*11 moderate-severe*

Note: All data designated as "other" and "missing data" were omitted from analysis.

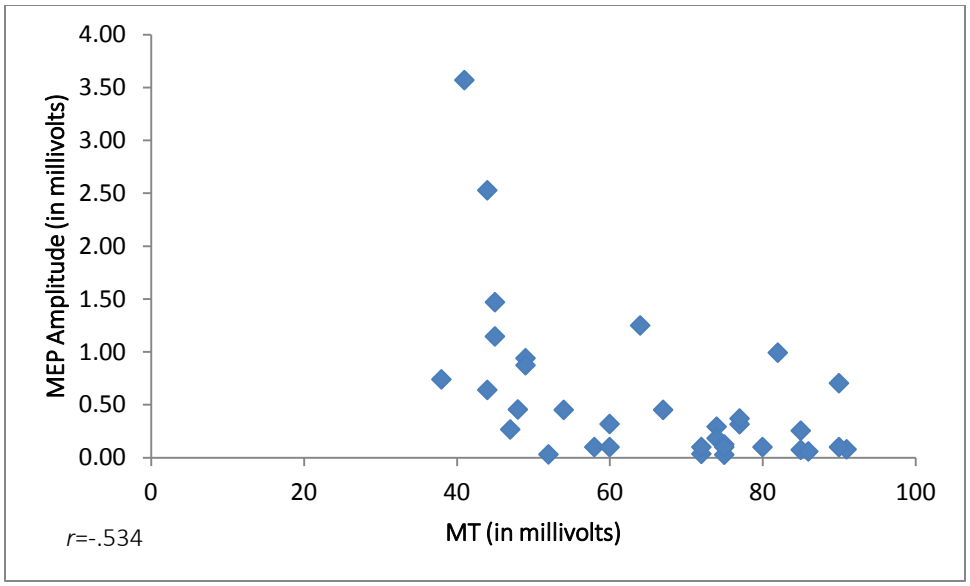

Figure 1: Correlation between MT and MEP Amplitude

As shown in Figure 2, significant and excellent-strength positive correlations were observed between MEP amplitude and ICF (r=.880, p<.001), such that participants who had higher MEP amplitudes displayed greater ICF (i.e., larger MEP amplitudes obtained during ICF testing). As shown in Figure 3, significant and moderately strong positive correlations were observed between MEP amplitude and ICI (r=.604, p<.001), such that participants who had higher MEP amplitude displayed less ICI (i.e., larger MEP amplitudes obtained during ICI testing).

Significant and fairly strong positive correlations were observed between ICF and ICI (r=.448, p=.011), such that participants who had greater ICF (i.e., larger MEP amplitudes obtained during ICF testing) displayed less ICI (i.e., larger MEP amplitudes obtained during ICI testing). (See Table 2.)

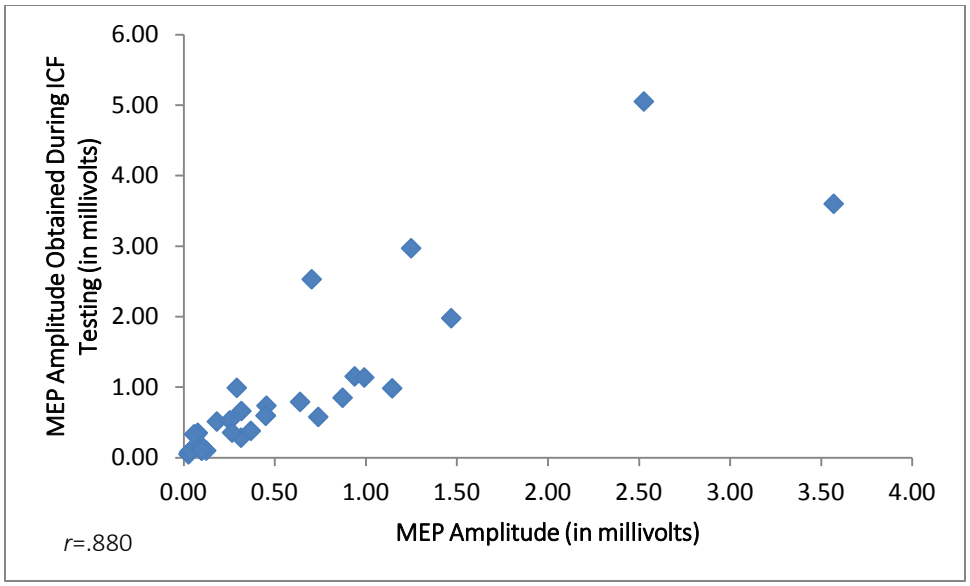

Figure 2: Correlation between MEP Amplitude and ICF

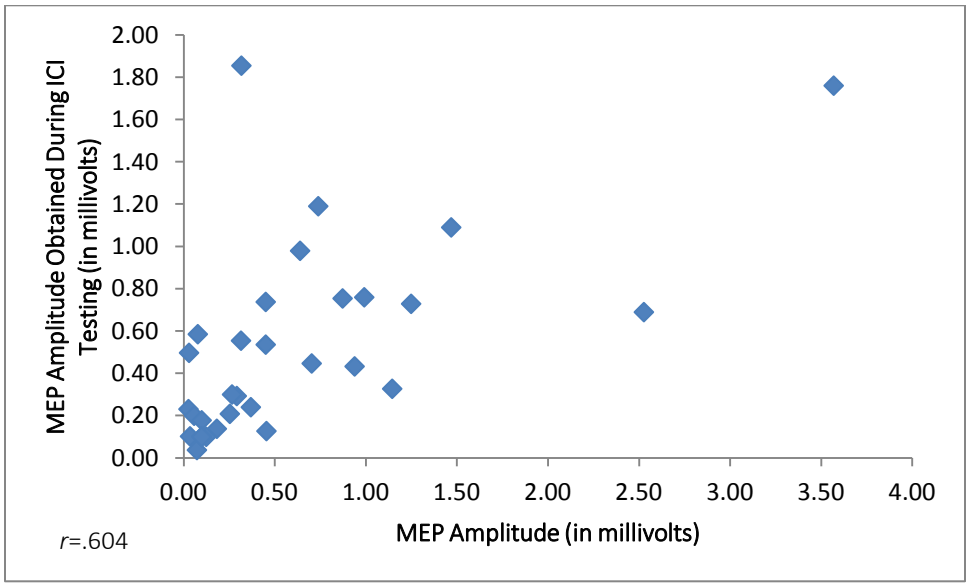

Figure 3: Correlation between MEP Amplitude and ICI

TABLE 2. Pearson Correlations among TMS, Grip Strength, Fugl-Meyer Upper Extremity Motor Score, and Chronicity

		MT	MEP	ICF	ICI	Grip	FM	Chronicity
MT	Pearson Correlation	1	-.534**	-.360*	-.473**	-.110	-.043	.161
	Sig. (2-tailed)		.001	.033	.007	.524	.806	.349
	N	36	34	35	31	36	35	36
MEP	Pearson Correlation	-.534**	1	.880**	.604**	.195	.173	-.058
	Sig. (2-tailed)	.001		.000	.000	.269	.336	.745
	N	34	34	34	31	34	33	34
ICF	Pearson Correlation	-.360*	.880**	1	.448*	.060	.213	.001
	Sig. (2-tailed)	.033	.000		.011	.733	.228	.994
	N	35	34	35	31	35	34	35
ICI	Pearson Correlation	-.473**	.604**	.448*	1	-.189	.126	.004
	Sig. (2-tailed)	.007	.000	.011		.310	.508	.981
	N	31	31	31	31	31	30	31
Grip	Pearson Correlation	-.110	.195	.060	-.189	1	.449**	-.174
	Sig. (2-tailed)	.524	.269	.733	.310		.006	.303
	N	36	34	35	31	37	36	37
FM	Pearson Correlation	-.043	.173	.213	.126	.449**	1	-.043
	Sig. (2-tailed)	.806	.336	.228	.508	.006		.802
	N	35	33	34	30	36	36	36
Chronicity	Pearson Correlation	.161	-.058	.001	.004	-.174	-.043	1
	Sig. (2-tailed)	.349	.745	.994	.981	.303	.802	
	N	36	34	35	31	37	36	37

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Relationships among Motor Performance Data

Significant and fairly strong positive correlations were observed between FM upper extremity motor and grip strength (r=.449, p=.006), such that participants with higher FM upper extremity motor scores displayed higher grip strength scores (Table 2). Significant and fairly strong positive correlations were observed between MAL Quality of Movement and FM upper

extremity motor (r=.450, p=.006), such that participants with higher MAL Quality of Movement scores displayed higher FM upper extremity motor scores. (See Table 3.)

TABLE 3. Spearman Correlations between Motor Activity Log Quality of Movement Score and TMS, Grip Strength, Fugl-Meyer Upper Extremity Motor Score, and Chronicity

		MAL	MT	MEP	ICF	ICI	Grip	FM	Chronicity
MAL	Correlation Coefficient	1.000	.172	-.151	-.057	-.191	.175	.450**	.456**
	Sig. (2-tailed)		.317	.395	.745	.302	.299	.006	.005
	N	37	36	34	35	31	37	36	37

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Relationships between Neurophysiological and Motor Performance Data

No significant relationships were observed between TMS measures of MT, MEP amplitude, ICI, and ICF and motor performance measures of grip strength, FM score, and MAL Quality of Movement score (Tables 2 and 3).

Neurophysiological Differences based on and Attribute Groupings

No significant differences were found in TMS measures of MT, MEP amplitude, ICI, and ICF using lesion location, hemisphere, age, chronicity, or stroke severity of the motor impairment as grouping variables. (See Tables 4-7.)

Relationships between Motor Performance and Attribute Data

A significant and fairly strong positive correlation was observed between MAL and chronicity (r=.456, p=.005), such that participants with higher MAL Quality of Movement scores were, in general, further from the onset of the stroke. (See Table 3.)

A MANOVA indicated a significant multivariate main effect for stroke severity of the motor impairment ($F_{7,22}$=4.046, p=.005). Univariate analyses indicated significant differences in grip strength based on stroke severity of the motor impairment (F_1=8.39, p=.007), with participants who had a mild stroke displaying higher grip strength scores (mean=11.04 kg,

SD=9.56 kg) than the moderate-severe group (mean=3.26 kg, *SD*=4.69 kg). (See Table 4 and Figure 4.) Significant differences were also observed in FM upper extremity motor scores based on stroke severity (F_1=21.781, p<.001), which confirms that our use of FM cutoff scores appropriately classified subjects into distinct severity categories. Participants who had a mild stroke displayed higher FM upper extremity motor scores (mean=51.15, *SD*=7.96) than participants who had a moderate-severe stroke (mean=33.30, *SD*=10.26). (See Table 4 and Figure 5.) Additionally, MEP amplitude approached significance based on stroke severity (p=.066). No other significant differences were observed in motor performance data based on stroke severity, hemisphere, lesion location, or age. (See Tables 5-7.)

TABLE 4. MANOVA for TMS, Grip Strength, Fugl-Meyer Upper Extremity Motor Score, and Chronicity Based on Stroke Severity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	MT	369.416[a]	1	369.416	1.344	.256
	MEP	2.032[b]	1	2.032	3.650	.066
	ICF	1.847[c]	1	1.847	1.391	.248
	ICI	.400[d]	1	.400	1.929	.176
	Grip	460.035[e]	1	460.035	8.394	.007
	FM	2212.504[f]	1	2212.504	21.781	.000
	Chronicity	485.435[g]	1	485.435	.324	.573

a. R Squared = .046 (Adjusted R Squared = .012)
b. R Squared = .115 (Adjusted R Squared = .084)
c. R Squared = .047 (Adjusted R Squared = .013)
d. R Squared = .064 (Adjusted R Squared = .031)
e. R Squared = .231 (Adjusted R Squared = .203)
f. R Squared = .438 (Adjusted R Squared = .417)
g. R Squared = .011 (Adjusted R Squared = -.024)

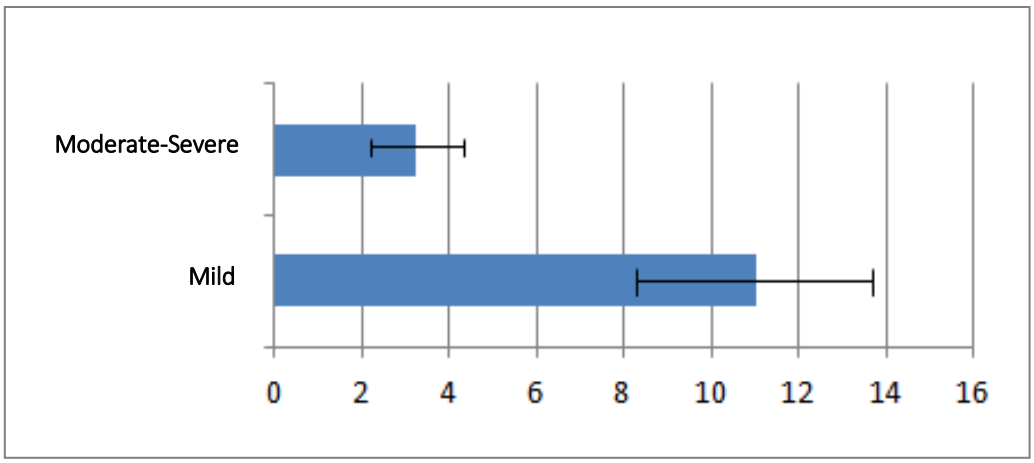

Figure 4: Mean Grip Strength Scores Based on Stroke Severity

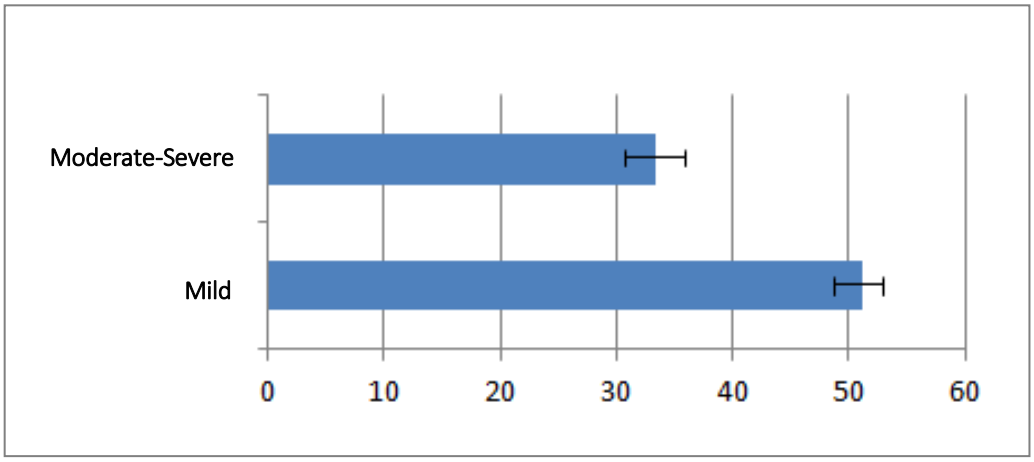

Figure 5: Mean Fugl-Meyer Upper Extremity Motor Score Based on Stroke Severity

TABLE 5. MANOVA for TMS, Grip Strength, Fugl-Meyer Upper Extremity Motor Score, and Chronicity Based on Lesion Location

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	MT	386.369[a]	1	386.369	1.387	.250
	MEP	.388[b]	1	.388	.580	.453
	ICF	.584[c]	1	.584	.380	.543
	ICI	.696[d]	1	.696	3.234	.084
	Grip	139.521[e]	1	139.521	2.973	.097
	FM	1.091[f]	1	1.091	.006	.940
	Chronicity	33.670[g]	1	33.670	.020	.887

a. R Squared = .053 (Adjusted R Squared = .015)
b. R Squared = .023 (Adjusted R Squared = -.016)
c. R Squared = .015 (Adjusted R Squared = -.024)
d. R Squared = .115 (Adjusted R Squared = .079)
e. R Squared = .106 (Adjusted R Squared = .071)
f. R Squared = .000 (Adjusted R Squared = -.040)
g. R Squared = .001 (Adjusted R Squared = -.039)

TABLE 6. MANOVA for TMS, Grip Strength, Fugl-Meyer Score, and Chronicity Data Based on Hemisphere

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	MT	629.342[a]	1	629.342	2.580	.121
	MEP	.109[b]	1	.109	.322	.576
	ICF	.826[c]	1	.826	.647	.429
	ICI	.011[d]	1	.011	.057	.814
	Grip	22.475[e]	1	22.475	.347	.561
	FM	500.111[f]	1	500.111	2.864	.104
	Chronicity	1268.616[g]	1	1268.616	.779	.386

a. R Squared = .097 (Adjusted R Squared = .059)
b. R Squared = .013 (Adjusted R Squared = -.028)
c. R Squared = .026 (Adjusted R Squared = -.014)
d. R Squared = .002 (Adjusted R Squared = -.039)
e. R Squared = .014 (Adjusted R Squared = -.027)
f. R Squared = .107 (Adjusted R Squared = .069)
g. R Squared = .031 (Adjusted R Squared = -.009)

Analyses comparing stroke severity groups on the outcomes, grip strength (p=.007) and FM upper extremity motor scores (p<.001) failed Levene's test of equality of error variances (see Table 8). Therefore, Kruskal-Wallis analyses were completed showing retained significance for

grip strength based on stroke severity (p=.023) and for FM upper extremity motor scores (p<.001) based on stroke severity (see Table 9).

TABLE 7. MANOVA for TMS, Grip Strength, Fugl-Meyer Score, and Chronicity Data Based on Age

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	MT	180.000[a]	1	180.000	.639	.431
	MEP	.229[b]	1	.229	.369	.549
	ICF	.626[c]	1	.626	.457	.505
	ICI	.270[d]	1	.270	1.274	.269
	Grip	8.565[e]	1	8.565	.121	.731
	FM	190.139[f]	1	190.139	1.094	.305
	Chronicity	530.450[g]	1	530.450	.355	.556

a. R Squared = .022 (Adjusted R Squared = -.013)
b. R Squared = .013 (Adjusted R Squared = -.022)
c. R Squared = .016 (Adjusted R Squared = -.019)
d. R Squared = .044 (Adjusted R Squared = .009)
e. R Squared = .004 (Adjusted R Squared = -.031)
f. R Squared = .038 (Adjusted R Squared = .003)
g. R Squared = .013 (Adjusted R Squared = -.023)

Table 8. Levene's Test of Equal Variance

	F	df1	df2	Sig.
MT	.048	1	28	.828
MEP	7.625	1	28	.010
ICF	3.055	1	28	.091
ICI	2.051	1	28	.163
Grip	10.555	1	28	.003
FM	6.763	1	28	.015
Chronicity	.000	1	28	.989

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

Kruskal-Wallis tests also were used in the case of the MAL measure considering these data are ordinal. Analyses indicated significant differences in MAL Quality of Movement scores based on stroke severity (p=.036) with participants who had mild stroke tending to have higher

MAL scores (median=2.97, minimum=1.50, maximum=4.46) than participants who had a moderate-severe stroke (median=2.40, minimum=1.31, maximum=3.96). See Tables 10 and 11. No other significant differences for MAL were found based on lesion location, hemisphere, or age. (See Table 10.)

TABLE 9. Kruskal-Wallis Tests for Grip Strength and Fugl-Meyer Upper Extremity Motor Score Based on Stroke Severity

Null Hypothesis	Test	Sig.	Decision
The distribution of Grip Strength is the same across categories of Severity.	Independent-Samples Kruskal-Wallis Test	.023	Reject the null hypothesis.
The distribution of FM is the same across categories of Severity.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

TABLE 10. Kruskal-Wallis Tests for Motor Activity Log Quality of Movement Score Based on Stroke Severity

Null Hypothesis	Test	Sig.	Decision
The medians of MAL Quality of Movement are the same across categories of Stroke Severity	Independent-Samples Kruskal-Wallis Test	.036	Reject the null hypothesis
The medians of MAL Quality of Movement are the same across categories of Lesion Location	Independent-Samples Kruskal-Wallis Test	.679	Retain the null hypothesis
The medians of MAL Quality of Movement are the same across categories of Hemisphere	Independent-Samples Kruskal-Wallis Test	.705	Retain the null hypothesis
The medians of MAL Quality of Movement are the same across categories of Age	Independent-Samples Kruskal-Wallis Test	.560	Retain the null hypothesis

Asymptotic significances are displayed. The significance level is .05.

TABLE 11. Descriptive Statistics of Motor Activity Log Quality of Movement Score Based on Stroke Severity

	Median	Minimum	Maximum
Mild			
MAL	2.97	1.50	4.46
Moderate-Severe			
MAL	2.40	1.31	3.96

DISCUSSION

This descriptive study explored the relationships among neurophysiological, motor performance, and attribute data in participants in the chronic stage of stroke. While there were significant relationships among neurophysiological variables (obtained by TMS) and within motor performance data, no significant relationships between neurophysiological data and motor performance data were observed. Considering attribute variables, only motor performance variables were observed to significantly differ based on stroke severity.

Relationships among Neurophysiological Variables

The significant negative relationship observed between affected-hemisphere MT and MEP supports previous work showing that higher MT typically is associated with lower MEP (Cortes et al., 2012; Liepert, 2006; Malcolm et al., 2014). This relationship makes sense considering there is resistance in the circuit resulting from the original pathology. If a higher-intensity signal is required before the threshold for excitation is crossed, then the MEP amplitudes in response to any given suprathreshold signal should be reduced by this same resistance.

The significant positive relationship observed between ICF and ICI adds to the literature and suggests that ICF and ICI are connected. A lesser degree of ICI, resulting in greater MEP amplitude measured peripherally and greater ICF (i.e., greater MEP amplitude during ICF tests) complement each other in increasing intracortical excitability post-stroke. However, the relationship is complicated considering less inhibition post stroke can be problematic if it implies spasticity and decreased motor control. Both Liepert (2006) and Malcolm et al. (2014)

demonstrated greater ICI (greater inhibition) in individuals without stroke. So while a positive correlation is shown in the current study and supports the notion that both ICF and ICI point to greater excitability, thought of as desirable, one must consider that greater cortical excitability after stroke could indicate pathology in the form of a release phenomenon as seen in the case of damage to the ventral lateral nucleus of the thalamus. The Honaga et al. (2013) finding that participants with greater ICI (i.e., smaller MEP amplitudes during ICI testing) displayed higher scores on the Stroke Impairment Assessment Set (SIAS) finger function test and the FM upper extremity motor test indicates greater inhibition is the normal state and less inhibition may indicate pathology.

It is important, as well, to consider that different findings regarding MEP amplitude and ICI after stroke may be a consequence of methodology used in the measurement. The significant positive relationship shown in the current work between MEP amplitude when stimulating the affected-hemisphere and ICI suggests that corticospinal (the delivery system when measuring MEP) and intracortical (signal origin) excitability are positively associated. This conflicts with prior research by Honaga et al. (2013), who found that affected-hemisphere MEP amplitude and ICI did not correlate and were indicative of corticospinal and intracortical excitability being unrelated. One explanation for this finding is that Honaga et al. (2013) obtained TMS measures from the affected extensor digitorum communis (EDC) muscle while the current study obtained TMS measures from the affected FDI, suggesting that the FDI may be more sensitive to corticospinal and intracortical excitability than the EDC. Additionally, in testing ICI, Honaga et al. (2013) based the sub-threshold stimulus intensity on MT obtained when the EDC was activated, and the supra-threshold stimulus intensity on MT obtained when the EDC was at

rest. As the current study based both the sub- and supra-threshold stimuli intensities on MT when the FDI was at rest, this suggests that measuring ICI based on resting MT (particularly of the FDI) is more sensitive to intracortical and corticospinal excitability than based on both resting and active MT of the EDC.

This study adds knowledge of the relationships between affected-hemisphere MT and ICF, which were significantly negatively related; between affected-hemisphere MT and ICI, which were significantly negatively related; and between affected-hemisphere MEP amplitude and ICF, which were significantly positively related. The significant negative relationships between MT and both ICF and ICI suggests that lower corticospinal excitability (high MT value) is associated with lower intracortical excitability. Moreover, the significant positive relationship between affected-hemisphere MEP amplitude and ICF suggests that higher corticospinal excitability is associated with higher intracortical excitability.

Relationships among Motor Performance Variables

The significant positive relationship between affected upper extremity FM motor score and affected upper extremity grip strength supports previous work by Cha et al. (2014), which showed that FM scores and grip strength scores improved together after transcranial direct current stimulation. The current study shows this relationship exists even before therapy. Massie et al. (2014) also demonstrated the relationship of FM motor performance and another biomechanical measure in their finding of positive significant associations between FM motor scores and various upper extremity range of motion measurements in their study of cyclic versus discrete reaching post-stroke.

The significant positive relationship between affected upper extremity FM motor scores and MAL Quality of Movement scores found in the current study also complements previous research (Takebayashi et al., 2015), suggesting that higher upper extremity motor performance on the FM is associated with participant-perceived amount of use (Takebayashi et al., 2015) and quality of movement (current study) of the affected upper extremity.

Significant relationships between MAL Quality of Movement scores and grip strength were not found, which conflicts with a previous study (Harris & Eng, 2007). Concerning the work of Harris and Eng (2007), who showed significant positive correlations between grip strength and both the Amount of Use and Quality of Movement scales of the MAL, one explanation for the current study's conflicting finding is that the current study examined individuals with lower grip strength scores (mean=6.47 kg) than those examined by Harris and Eng (mean=13.0 kg). Such a discrepancy among grip strength scores may suggest that for a relationship to emerge between grip strength and self-perceived quality of movement, individuals must have greater capacity for grip in the affected hand.

Relationships between Neurophysiological and Motor Performance Data

No significant relationships between affected-hemisphere neurophysiological and affected upper extremity motor performance data were observed. Concerning affected-hemisphere MT and MEP amplitude, this finding conflicts with previous research showing that lower MT and larger MEP amplitude correlates with better motor function (Brouwer & Schryburt-Brown, 2006; Koski et al., 2004; Liepert, 2006). Possible explanations for the conflicting information shown in the current study may include different measures of motor performance used (FM upper extremity motor, grip strength, Quality of Movement scale of the

MAL) as opposed to Brouwer and Schryburt-Brown (2006), who used the Purdue pegboard task, keyboard tapping task, and FDI muscle strength task as measures. Another possible explanation may be that baseline scores may not correlate at baseline, but therapy-induced change in baseline scores of the measures may moderately or strongly correlate—as was demonstrated in studies by Koski et al. (2004) and Liepert (2006).

Concerning affected-hemisphere ICI and ICF, the current study supports previous work done by Liepert (2006) who found no relationship between ICI or ICF and motor performance as measured by both the Quality of Movement and Amount of Use scales of the MAL and the WMFT. Other research has demonstrated contradictory findings in both positive relationships between ICI and motor performance measures (Liuzzi et al., 2014; Marconi et al., 2011) and negative relationships between ICI and motor function measures (Honaga et al., 2013).

Relationships between Neurophysiological and Attribute Data

No significant differences were observed considering affected-hemisphere neurophysiological measures comparing cortical to subcortical lesion location. While some research supports this finding, particularly with MT (Honaga et al., 2013) and MEP amplitude (Liepert, 2006), research by Marconi et al. (2011) found that participants with a cortical lesion had lower MT than those with subcortical lesions. One explanation for this difference is that the current study included participants with both cortical and subcortical involvement in the cortical group while Marconi et al. (2011) excluded all participants with both cortical and subcortical involvement so that each group consisted of purely cortical or purely subcortical involvement.

No significant differences were observed in affected-hemisphere neurophysiological measures based on chronicity. The current study supports previous work by Honaga et al. (2013)

who found no correlation between MT and chronicity, but conflicts with their finding that ICI significantly and inversely correlated with chronicity.

No significant differences were observed in affected-hemisphere neurophysiological measures based on hemisphere. This finding supports previous research by Marconi et al. (2011) and suggests that cortical and corticospinal excitability in the chronic stage of stroke are independent of hemispheric lesion location.

No significant differences were observed in affected-hemisphere neurophysiological measures based on age groupings. As no evidence could be found to either support or refute this finding, the lack of age-related differences in any of the TMS-based measures in the current study suggests that cortical and corticospinal excitability are indiscernible in groupings over versus under 65 years of age.

No significant differences were observed in affected-hemisphere neurophysiological measures based on severity of the affected upper extremity motor impairment. This finding is surprising considering individuals with stroke tend to have higher MT and lower MEP, together indicating less excitability, than individuals without stroke. However, severity of the motor impairment was measured by the FM, which is a more global motor function assessment as opposed to TMS measures, which are measures of corticospinal (MT and MEP amplitude) and cortical (ICI and ICF) excitability. Indeed, looking even just at MT in the current study, ranges in MT of those with milder strokes (41-86) did not notably differ from those with moderate-severe strokes (38-91). Therefore, the lack of a difference in the current study suggests that cortical and corticospinal excitability are quite variable across different levels of severity and may not be sensitive measures of actual motor performance.

Relationships between Motor Performance and Attribute Data

No significant differences were observed in affected upper extremity motor performance based on cortical or subcortical lesion location. This finding supports prior research by Liepert (2006) and Honaga et al. (2013), who found no significant differences in motor performance based on cortical or subcortical lesion location. However, this finding conflicts with research by Marconi et al. (2011), who observed that participants with cortical lesions had better motor performance outcomes in the affected upper extremity than participants with subcortical lesions. As with the explanation between TMS and lesion location, an explanation for this may be that Marconi et al. (2011) excluded individuals who had both cortical and subcortical involvement while the current study included individuals with both cortical and subcortical involvement into the cortical group. Additionally, Marconi et al. (2011) used different motor performance measures (WMFT and Motricity Index for the upper limbs) as compared with the current study's use of the FM upper extremity motor scores, MAL Quality of Movement scores, and grip strength. Such differences suggest that differences in motor performance depend on pure divisions of cortical and subcortical stroke involvement as well as the motor performance assessments used.

No significant relationships were observed in affected upper extremity grip strength or FM upper extremity motor scores with chronicity; but a significant positive relationship was observed between affected upper extremity MAL Quality of Movement scores and chronicity. This finding suggests that the further out from stroke, the higher the self-perceived quality of movement of the affected arm in functional tasks performed. This finding conflicts with prior research by Gauthier et al. (2014), who found no correlations between chronicity and perceived

motor performance, as measured by the MAL Quality of Movement scale. As with the comparison between neurophysiological measures and chronicity, an explanation for the differing findings between Honaga et al. (2013) and the current study may be the differing means of time post-stroke. Comparing the current study's findings to Gauthier et al. (2014), an explanation may be that measures of motor performance in Gauthier et al. (2014) were analyzed over both pre- and post-CIMT while in the current study, they were taken at pretest and unconditioned by therapy. Such a difference may suggest that without therapy, individuals with stroke may perceive the quality of their movement on the MAL better the more time they have had beyond the onset of their stroke. In contrast, with therapy, improvements on both scales of the MAL may be independent from length of time post-stroke and related more to the gains from therapy, regardless of time.

No significant relationship was observed in affected upper extremity motor performance based on being older or younger than 65 years. This finding conflicts with research obtained in acute stages of stroke, which demonstrated that individuals who were older than 65 had lower FM scores than individuals who were younger than 65 years (Ferrucci et al., 1993). However, the current study examined such age differences in chronic stages of stroke, suggesting that by chronic stages, motor performance based on FM score does not depend on age. Concerning MAL, Fritz et al. (2006) found in a CIMT study of individuals in chronic stages of stroke, age (though not split into groups of over or under 65 years) was found to be inversely related to the MAL Amount of Use scale. As the current study used the MAL Quality of Movement scale, this may suggest that differences in perceived motor performance based on age are related more to perceived amount of use rather than perceived quality of movement.

Significant differences were found in affected upper extremity grip strength, FM upper extremity motor score, and MAL Quality of Movement score based on severity of the motor deficit, with participants with milder strokes having better scores on each. These findings are consistent with previous research by Harris and Eng (2006) who found that grip strength and MAL Quality of Movement and Amount of Use scores were lower in individuals with severe strokes (measured by FM scores) than in those with mild strokes. Not surprisingly, each of these findings support the notion that motor performance and severity of the motor impairment are related.

Limitations

The current study is limited by the small sample size and the unequal amounts of participants in each of the stroke severity, lesion location, age, and hemisphere groups. Additionally, in the division of the cortical and subcortical groups, some participants in the cortical group also had subcortical involvement, which may have confounded the results. Future research should include a larger sample size with groups of more equal numbers as well as groups of purely cortical and purely subcortical lesion locations.

Conclusions

The current study is the first to examine such a large number of variables to provide a more complete picture of how pre-therapy neurophysiological measures associate with each other and with motor performance and attribute measures. Significant relationships were found within neurophysiological and within motor performance measures in chronic stages of stroke. However, significant relationships between neurophysiological and motor performance measures and between neurophysiological and attribute measures were not supported by this

study, suggesting that neurophysiological measures are not sensitive measures of motor performance, nor are they related to attribute measures. Regarding relationships between attribute and motor performance measures, stroke severity was observed to have the greatest influence on each of the motor performance measures: Individuals with mild severity of the motor impairment performed better on motor performance measures than individuals with moderate-severe motor impairments. As overall study findings both support and conflict with prior research, more research is needed to better elucidate these relationships and gain better understanding of how cortical excitability, motor performance, and attributes are connected.

REFERENCES

American Occupational Therapy Association (AOTA). (2013). *Recovering from stroke.* Retrieved from http://www.aota.org/about-occupational-therapy/participants-clients/adults/stroke/ recoveringfromstroke.aspx

Anand, S., & Hotson, J. (2002). Transcranial magnetic stimulation: Neurophysiological applications and safety. *Brain and Cognition, 50*(3), 366-386.

Arya, K.M., Pandian, S., Verma, R., & Garg, R.K. (2011). Movement therapy induced neural reorganization and motor recovery in stroke: A review. *Journal of Bodywork & Movement Therapies, 15,* 528-537.

Brouwer, B.J., & Schryburt-Brown, K. (2006). Hand function and motor cortical output poststroke: Are they related? *Archives of Physical Medicine & Rehabilitation, 87,* 627-634.

Byl, N., Roderick, J., Mohamed, O., Hanny, M. Kotler, J., Smith, A., ... Abrams, G. (2003). Effectiveness of sensory and motor rehabilitation of the upper limb following the principles of neuroplasticity. *Neurorehabilitation and Neural Repair, 17*(3), 176-191.

Centers for Disease Control (CDC). (2015). *Stroke facts.* Retrieved from http://www.cdc.gov/stroke/facts.htm

Cha, H., Ji, S., Kim, M., & Chang, J. (2014). Effect of transcranial direct current stimulation of function in participants with stroke. *Journal of Physical Therapy Science, 26*(3), 363-365.

Chen, R. (2004). Interactions between inhibitory and excitatory circuits in the human motor cortex. *Experimental Brain Research, 154*(1), 1-10.

Cortes, M., Black-Schaffer, R.M., & Edwards, D.J. (2012). Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: An overview for neurorehabilitation clinicinas. *Neuromodulation, 15*(4), 316-325.

Cramer, S.C., Sur, M., Dobkin, B.H., O'Brien, C., Sanger, T.D., Trojanowski, J.Q., Rumsey, J.M., … Vinogradov, S. (2011). Harnessing neuroplasticity for clinical applications. *Brain, 134*(6), 1591-1609.

Duncan, P.W., Lai, S.M., & Keighley, J. (2000). Defining post-stroke recovery: implications for design and interpretation of drug trials. *Neuropharmacology, 39*(5), 835-841.

Edwards, J.D., Meehan, S.K., Linsdell, M.A., Borich, M.R., Anbarani, K., Jones, P.W., … Boyd, L.A. (2013). Changes in thresholds for intracortical excitability in chronic stroke: More than just altered intracortical inhibition. *Restorative Neurology and Neuroscience, 31,* 693-705.

Ferrucci, L., Bandinelli, S., Guralnik, J.M., Lamponi, M., Bertini C., Falchini, M., & Baroni, A. (1993). Recovery of functional status after stroke: A postrehabilitation follow-up study. *Stroke, 24,* 200-205.

Fritz, S.L., Light, K.E., Clifford, S.N., Patterson, T.S., Behrman, A.L., & Davis, S.B. (2006). Descriptive characteristics as potential predictors of outcomes following constraint-induced movement therapy for people after stroke. *Physical Therapy, 86*(6), 825-832.

Gauthier, L.V., Mark, V.W., Taub, E., McCullars, A., Barghi, A., Rickards, T., … Uswatte, G. (2014). Motor recovery from constraint induced movement therapy is not constrained by extent of tissue damage following stroke. *Restorative Neurology and Neuroscience, 32,* 755-765.

Gauthier, L.V., Taub, E., Perkins, C., Ortmann, M., Mark, V.W., & Uswatte, G., (2008). Remodeling the brain: Plastic structural brain changes produced by different motor therapies after stroke. *Stroke, 39*(5), 1520-1525.

George, M.S., & Belmaker, R.H. (2007). *Transcranial magnetic stimulation in clinical psychiatry.* Arlington, VA: American Psychiatric Publishing, Inc.

Gladstone, D.J., Danells, C.J., & Black, S.E. (2002). The Fugl-Meyer assessment of motor recovery after stroke: A critical review of its measurement properties. *Neurorehabilitation and Neural Repair, 16*(3), 232-240.

Hallett, M. (2007). Transcranial magnetic stimulation: A primer. *Neuron, 55*(2), 187-199.

Harris, J.E., & Eng, J.J. (2006). Individuals with the dominant hand affected following stroke demonstrate less impairment than those with the nondominant hand affected. *Neurorehabilitation and Neural Repair, 20*(3), 380-389.

Harris, J.E., & Eng, J.J. (2007). Paretic upper-limb strength best explains arm activity in people with stroke. *Physical Therapy, 87*(1), 88-97.

Honaga, K., Fujiwara, T., Tsuji, T., Hase, K., Ushiba, J., & Liu, M. (2013). State of intracortical inhibitory interneuron activity in participants with chronic stroke. *Clinical Neurophysiology, 124,* 364-370.

Hosomi, K., Kishima, H., Oshino, S., Hirata, J., Tani, N., Maruo, T., … Saitoh, Y. (2013). Cortical excitability changes after high-frequency repetitive transcranial magnetic stimulation for central poststroke pain. *Pain, 154,* 1352-1357.

Jang, S.H. (2013). Motor function-related maladaptive plasticity in stroke: A review. *NeuroRehabilitation, 32,* 311-316.

Koski, L., Mernar, T.J., & Dobkin, B.H. (2004). Immediate and long-term changes in corticomotor output in response to rehabilitation: Correlation with functional improvements in chronic stroke. *Neurorehabilitation and Neural Repair, 18*(4), 230-249.

Liepert, J. (2006). Motor cortex excitability in stroke before and after constraint-induced movement therapy. *Cognitive Behavioral Neurology, 19*(1), 41-47.

Liuzzi, G., Horni, V., Lechner, P., Hoppe, J., Heise, K., Zimerman, M., … Hummel, F.C. (2014). Development of movement-related intracortical inhibition in acute to chronic subcortical stroke. *Neurology, 82,* 198-205.

Malcolm, M.P., Vaughn, H.N., & Greene, D. (2014). Inhibitory and excitatory motor cortex dysfunction persists in the chronic post-stroke recovery phase. *Journal of Clinical Neurophysiology Publish Ahead of Print.*

Marconi, B., Filippi, G.M., Koch, G., Giacobbe, V., Peccioli, C., Versace, V., … Caltagirone, C. (2011). Long-term effects on cortical excitability and motor recovery induced by repeated muscle vibration in chronic stroke participants. *Neurorehabilitation and Neural Repair, 25*(1), 48-60.

Massie, C.L., Malcolm, M.P., Greene, D.P., & Browning, R.C. (2014). Biomechanical contributions of the trunk and upper extremity in discrete versus cyclic reaching in survivors of stroke. *Topics in Stroke Rehabilitation, 21*(1), 23-32.

McCormack, G. (2009). How occupational therapy influences neuroplasticity. *OT Practice, 14*(7), CE-1—CE-7.

Orchanian, D.P., & Jamison, P.W. (2012). Cerebrovascular accident. In B.J. Atchison & D.K. Dirette (Eds.), *Conditions in occupational therapy: Effect on occupational performance* (4th ed.,

pp. 127-152). Philadelphia, PA: Lippincott Williams & Wilkins.

Perocheau, D., Laroche, F., & Perrot, S. (2014). Relieving pain in rheumatology participants: Repetitive transcranial magnetic stimulation (rTMS), a developing approach. *Joint Bone Spine, 81*(1), 22-26.

Platz, T., Pinkowski, C., van Wijck, F., Kim, I.H., di Bella, P., & Johnson, G. (2005). Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer test, action research arm test, and box and block test: A multicenter study. *Clinical Rehabilitation, 19*(4), 404-411.

Pollock, A. Farmer, S.E., Brady M.C., Langhorne P. Mead G.E., Mehrholz, J., & van Wijck F. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews,* Issue 11. Art. No.: CD01010820. DOI:10.1002/14651858.CD010820.pub2.

Portney, L.G., & Watkins, M.P. (2000). *Foundations of clinical research: Applications to practice* (2nd ed.). Upper Saddle River, NJ: Prentice-Hall, Inc.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., & the Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039.

Takebayashi, T., Amano, S., Hanada, K., Umeji, A., Takahashi, K., Marumoto, K., … Domen, K. (2015). A one-year follow-up after modified constraint-induced movement therapy for chronic stroke participants with paretic arm: A prospective case series study. *Topics in Stroke Rehabilitation, 22*(1), 18-25.

Tortora, G.J., & Derrickson, B. (2009). *Principles of anatomy and physiology* (12th ed.). Hoboken, NH: John Wiley & Sons, Inc.

Uswatte, G., Taub, E., Morris, D., Light, K., & Thompson, P.A. (2006). The Motor Activity Log-28: Assessing daily use of the hemiparetic arm after stroke.

Van der Lee, J.H., Beckerman, H., Knol, D.L., de Vet, H.C.W., & Bouter, L.M. (2004). Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic participants. *Stroke, 35*(6), 1410-1414.

Wagner, J.M., Rhodes, J.A., & Patten, C. (2008). Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. *Physical Therapy, 88*(5), 652-663.

Whatisneuroplasticity.com. (2010). *History of neuroplasticity.* Retrieved from http://www.whatisneuroplasticity.com/history.php.

Woodbury, M.L., Velozo, C.A., Richards, L.G., & Duncan, P.W. (2013). Rasch analysis staging methodology to classify upper extremity movement impairment after stroke. *Archives of Physical Medicine and Rehabilitation, 94,* 1527-1533.