DISSERTATION

THE ROLE OF REACHING AND NON-INVASIVE BRAIN STIMULATION FOR APPLICATIONS IN STROKE REHABILITATION

Submitted by

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ABSTRACT

THE ROLE OF REACH AND NON-INVASIVE BRAIN STIMULATION FOR APPLICATIONS IN STROKE REHABILITATION

Upper extremity motor impairments resulting from the neural damage caused by a stroke are often the focus of rehabilitation efforts. Research has demonstrated the plastic potential of the brain to change and reorganize following neurologic injury leading to conceptual shifts in stroke rehabilitation. These shifts include implementing structured, intensive protocols that are based on neurophysiologic, motor control, and motor learning principles to promote use-dependent plasticity. The following investigation is in response to the call from several prominent reviews for research to address specific mechanism based questions to advance stroke rehabilitation. Experiments were conducted to address two aims: the first aim was to determine how reaching task structure influences motor control strategies in survivors of stroke; and the second aim was to determine the effects of non-invasive motor cortex stimulation triggered by voluntary muscle activation to promote use dependent plasticity. Collectively, these studies provide a comprehensive investigation of how certain characteristics of interventions (e.g., the structure of the task) can influence

motor control and neurophysiological outcomes in survivors of stroke. The first aim was accomplished with kinematic motion analysis methods to determine how reaching movement patterns were generated by survivors of stroke, and if differences occurred when reaching discretely versus cyclically. The majority of the survivors of stroke in this study were able to maintain continuous, cyclic motion without dwelling periods between movements. The results demonstrated that survivors of stroke use a distinct movement pattern during cyclic reaching compared to when performing discrete reaching, i.e., significantly more trunk rotation. We further determined that muscle activation patterns were generally less in the stroke-affected side for muscles in the shoulder girdle (e.g., anterior and posterior deltoid). These results suggest that the incorporation of cyclic reaching tasks may be an important aspect of interventions and assessments because it requires the continuous integration of afferent feedback with the efferent (motor) output to sustain goal-directed reaching. The second aim was to investigate the impact of a novel motor cortex stimulation paradigm, termed functional-rTMS, on motor control and neurophysiologic measures. During functional-rTMS, subjects were required to actively trigger each train of stimulation by sufficiently generating muscle activity in a lateral pinch task. We found that subjects responded differently to functional-rTMS compared to passive-rTMS, i.e., stimulation delivered while subjects were relaxed. Following functional-rTMS, subjects had less inhibition and more facilitation of neural networks in the primary motor cortex. We also observed a differential effect of functional-rTMS on muscle representations such that the agonist was

preferentially modulated. The results of this study provide initial support for the potential to use functional-rTMS to modulate specific muscle groups within the same representation for survivors of stroke who often experience imbalances in flexion and extension in the upper extremity. Taken together, this collection of studies informs clinical researchers of a number of important mechanisms that can be incorporated into upper extremity stroke rehabilitation. Subjects who would likely qualify for intensive interventions are able to generate cyclic reaching without effects on motor performance. Incorporating such tasks within clinical interventions provides a learning opportunity to incorporate afferent feedback with efferent/motor output while completing repetitions. Secondly, functional-rTMS should be further explored with specific attention to the potential benefits of the differential effects on agonist versus antagonist muscle groups.

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DEDICATION

To my late grandfather, who had a zest for life and approached his career as his life rather than ‘work’. He was truly the epitome of embracing a career with such passion that you never work a day in your life. He was passionate and committed – qualities that I continue to admire and personally strive to achieve. He portrayed a proper work ethic, and the drive and determination required to achieve success in life. Our last conversation was related to starting my doctorate – I know that he wanted to see me graduate and I dedicate this dissertation to him.

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CHAPTER I INTRODUCTION

Stroke remains the leading cause of adult long-term disability in the United States, and often severely impacts upper extremity function (1). Research demonstrating the plastic potential of the brain to change and reorganize has resulted in conceptual shifts in stroke rehabilitation. One of the conceptual shifts has been the use of structured and intense interventions that are based on neurophysiologic, motor control, and motor learning principles to promote use-dependent plasticity. Although evidence suggests that intensive interventions are efficacious, ascertaining which components of an intervention are responsible for post intervention improvements is difficult to answer. Several recent prominent reviews have called for in-depth mechanistic research in stroke rehabilitation to address such difficulties (2-7). A systematic approach to further investigate mechanisms critical for neurorehabilitation is warranted in two distinct areas: 1. identifying the differences in motor control strategies based on the task structure for reaching interventions, and 2. determine the potential to increase the degree of use-dependent plasticity with non-invasive brain stimulation (repetitive transcranial magnetic stimulation, rTMS) paired with voluntary muscle activation in a novel protocol, termed functional-rTMS.

Motor control impairments post-stroke impact upper extremity function and the ability to generate coordinated reach, and these impairments are often the focus for neurorehabilitation interventions. Advancements in research the past

few decades have facilitated the opportunity to better understand how interventions or aspects of interventions impact underlying mechanisms responsible for the recovery from stroke. For example, developments in motion analysis systems and processing have facilitated a more thorough ability to describe and characterize movements post-stroke. Additionally, technologies like transcranial magnetic stimulation (TMS) and rTMS offer the ability to study the brain non-invasively and potentially provide therapeutic paradigms to foster improvements in motor control. These advancements provide the opportunity to rigorously and thoroughly investigate mechanisms that may aid in the processes of recovery from stroke, and ultimately lead to more efficacious interventions for survivors of stroke. The following studies are in direct response to the need for more mechanism based research in stroke rehabilitation by addressing a critical gap in the understanding of motor control strategy differences as the task structure is altered, and by providing new knowledge in regards to a novel stimulation paradigm.

Research has demonstrated that structured, specific, and intensive training protocols increase upper extremity functional capacity in survivors of stroke (8, 9), yet the impact of task structure (e.g. specific tasks performed during these protocols) on motor control strategies has received limited attention. For example, is there a difference in movement strategies if a reaching task is discrete compared to cyclic? This is an important consideration for stroke rehabilitation because both types of reaching have been employed in structured therapy. Discrete reaching predominates in constraint induced therapy (CIT), a

complex, multifaceted intervention designed to increase amount of hemiparetic arm use through massed practice and restraint of the less-affected side. In contrast, cyclic reaching is often used during interventions with rhythmic auditory stimulation (RAS) that combines auditory-motor entrainment with repetition. We have previously demonstrated that movement strategy changes post-intervention are not consistent across these two interventions (8, 10), suggesting that the task structure may be an important consideration. Following CIT, participants continued to rely on compensatory trunk motion during a forward reaching task, whereas trunk motion decreased following an RAS protocol. A quantitative description of how discrete vs. cyclic reaching is generated in survivors of stroke will facilitate the development and refinement of interventions and assessments.

An essential feature of the brain is its capacity to adapt to experiences, termed use-dependent plasticity (UDP). In the context of a stroke, the concepts of UDP span the continuum of maladaptive changes to the promotion of adaptive processes through rehabilitation efforts (11, 12). Research with animals (13-16) and humans (17, 18) has highlighted a number of presumed neurophysiological mechanisms responsible for UDP. These can include structural changes at the neuronal level and/or changes in excitability levels. Structural changes following motor skill learning in rats has included increased dendritic branching, dendritic spine density, and synapse formation (12). Changes in the excitability level can encompass synaptic efficacy resulting in long-term potentiation (LTP) or long-term depression (LTD) (17, 19). Although direct evidence of these changes in humans may not yet possible, they are presumed mechanisms of action

responsible for UDP. Repetitive transcranial magnetic stimulation (rTMS) paradigms have been implicated as non-invasive methods to modulate cortical excitability by presumably changing synaptic efficacy (19). The modulation as a result of rTMS protocols can only be studied at the response level of large neuronal networks in humans, and the synaptic efficacy changes at the neuronal level must be inferred. Although this presents as a limitation, a number of methodological techniques provide insight into the potential changes. For example, paired-pulse TMS techniques can reveal information relating to the inhibitory and facilitatory cortical networks (20, 21), and how rTMS can influence excitability modulation through these networks (19).

The potential to use non-invasive cortical stimulation to potentiate UDP in survivors of stroke is of clinical interest and is the second area requiring systematic investigation. Functional-rTMS may enhance the degree of UDP by augmenting the excitability of the motor circuits already engaged during a voluntary motor task. The voluntary, active engagement of motor cortical areas at the same time as applying an rTMS train represents a distinct difference to many of the rTMS protocols that have been applied passively, i.e., no active involvement by the subject. Although functional-rTMS is supported theoretically and with initial evidence (22-24), a more precise quantification of the neurophysiologic changes is required to better understand the impact of this technique on survivors of stroke.

CHAPTER II – MANUSCRIPT I

Title: Kinematic motion analysis and muscle activation patterns of continuous reaching in survivors of stroke.

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Manuscript Abstract

Background: Coordinated reaching requires continuous interaction between the efferent motor output and afferent feedback, and this interaction may be significantly compromised following a stroke. Purpose: This study sought to characterize how survivors of stroke generate continuous, goal-directed reaching. Methods: Sixteen survivors of stroke completed functional testing of the stroke-affected side and a continuous reaching task between two targets with both sides. Motion analysis and electromyography data were collected to determine segmental contributions to reach (e.g., amount of compensatory trunk), spatiotemporal parameters (e.g., peak velocities), and muscle activation patterns (MAP). Repeated-measures ANOVAs compared how survivors of stroke reach with the stroke-affected versus less-affected sides. Correlations were determined between kinematic outcomes and functional ability. Results: Participants used significantly more trunk movement and less shoulder flexion and elbow extension when reaching with the stroke-affected side. This corresponded with less muscle activity in the proximal musculature including the anterior, middle, and posterior deltoid on the stroke-affected side. There were significant correlations between the segmental contributions to reach, functional ability, and muscle activation patterns. Conclusions: Survivors of stroke generate reduced MAPs in the stroke-affected side corresponding to altered segmental kinematics and function ability. These findings suggest that impairments in the ability to generate sufficient MAPs may contribute to the difficulty in generating continuous reaching motions.

Introduction

The ability to generate coordinated reaching is a fundamental component of activities of daily living. Following a stroke, motor impairments in the upper-extremity (UE) often compromise reaching ability, contributing to decreased autonomy and quality of life for the survivor of stroke. Continuous reaching (CR) incorporates a complex interaction of cyclic and translatory components (25) requiring continual interaction between neural processes and the musculoskeletal system (26). Despite the necessity to incorporate CR in daily life, the majority of stroke-related research has focused on discrete reaching paradigms, i.e., a single defined start and end point (27-30). The findings of compensatory trunk movement, altered inter-joint coordination, and segmented movements, (28, 31) among others, have increased the understanding of motor control impairments impacting ballistic and quick movements, yet may not characterize the ability to generate CR. Examining how survivors of stroke generate CR is necessary to identify mechanisms that may facilitate rehabilitation efforts (2).

Cyclic reaching requires constant interaction between efferent motor output and afferent feedback (32), and should not be viewed as a concatenation of discrete reaching. Research in neurologically-intact populations has demonstrated reciprocal movements reversing motion at target contacts rather than terminating motion on a target are likely regulated by distinct neural commands (33, 34). Hogan and Sternad (35) have made significant contributions to formally defining reciprocal movements as “movements with

recurring configurations…" and discrete movements as movements bound by a period of no movement (p. 25). These distinctions highlight differences not only in understanding but also in the experimental methodologies used to study motor control theories to explain aspects of motor performance. For example, concepts of generalized motor programs can explain discrete tasks, yet a dynamic-systems approach can explain cyclical tasks (36). Thus rejecting one theory in favor of another is not yet justified (36).

The theoretical basis for cyclic reaching in neurologically-intact populations continues to be updated, (25, 34, 37-39) and the unique properties of reciprocal reaching have been well-documented in neurologically-intact populations (37, 40, 41). Smits-Engelsman et al.(37) demonstrated that cyclic movements resulted in superior movement speed and quality such that speed can be increased twice as much before a decrease in accuracy compared to discrete tasks (41). Dounskaia et al.(40) demonstrated that movements are smoother when reaching continuously between two targets. Movement speed and smoothness are two characteristics of discrete reaching impacted by stroke, yet limited evidence exists to describe CR. Given the potential benefits of cyclic reaching in neurologically-intact populations, an investigation of how damage to the nervous system may impair the ability to generate CR is warranted. This type of evidence may support the use of CR tasks in stroke UE rehabilitation if the benefits of cyclic reaching are maintained following a stroke.

Currently, there is limited understanding of how survivors of stroke perform CR (42). The neural damage caused by a stroke can result in a vast

array of pathophysiological symptoms such as hemiparesis or altered muscle tone that may significantly impair motor control of the UE (43, 44). These impairments, along with non-neural, musculoskeletal changes such as muscle atrophy, likely influence the ability to incorporate the affected UE in functional tasks because movements can be difficult to generate, maintain, and control. During forward reaching discrete tasks, survivors of stroke often use compensatory trunk movement and less elbow extension compared to neurologically-intact controls (28). These segmental contributions coincide with altered spatiotemporal parameters including extended movement durations, decreased peak velocity, and more segmented movements. The neural damage caused by a stroke may interfere with the ability to continuously generate efferent motor output while incorporating afferent feedback such that performance is significantly impaired or unsuccessful. For example, the inability to generate CR may be evidenced by long dwell periods at target contact in contrast to the smooth accelerations and decelerations between target contacts with no dwell time seen in normal CR. Investigating CR in the stroke affected UE is an important area for neurorehabilitation for two reasons: 1. determines motor control impairments in the ability to generate CR and how that may influence functional ability; and 2. further develops the evidence base for interventions that incorporate CR.

This study sought to characterize kinematics and muscle activation patterns of CR in survivors of stroke by comparing the less-affected to the more-affected side. We hypothesized that subjects engaged in a CR task would

demonstrate a less coordinated reach with a greater contribution of trunk movement and less use of the shoulder and elbow when using the stroke-affected side compared to the less-affected side. Our goal is to provide a better understanding of how coordinated UE movement is executed in survivors of stroke to assist clinicians and researchers in the development and refinement of structured UE interventions to target specific motor impairments.

Methods

Participants. Sixteen survivors of stroke (9 male; 8 left cerebral vascular accident) with a mean age of 66.6 (SD±11.6) years participated and gave written consent in accordance with the policies of the local institutional review board. Table 1.1. summarizes participant demographics. Participants met the following inclusion criteria: at least 6 months post-stroke; at least 10° of active wrist extension and approximately 30° of active shoulder flexion, both in the stroke-affected side. Exclusion criteria included: other neurologic conditions (e.g., multiple sclerosis, Parkinson's disease); injections treating spasticity within 3 months of participation; and Mini-Mental State Exam score less than 24 (45). These inclusion criteria are typical for subjects recruited for intensive therapeutic interventions. Participants completed a functional assessment of the stroke-affected side including the upper extremity portion of the Fugl-Meyer (FM) (46) and the Box and Block Test (BBT). The FM has known psychometric properties, (47) and the BBT has been evaluated as an outcome measure for survivors of stroke (48, 49).

Motion capture setup and outcomes. See Figure 1.1. for experimental setup. Participants sat comfortably in a chair and were asked to reach between two targets 0.35m apart in a parasagittal plane at a height of 0.71m. The initial starting position was approximately 0° of shoulder flexion, 90° of elbow flexion, and a neutral trunk position with the close target located approximately 25cm anterior to the elbow. Participants were given 1-2 practice trials to become familiar with the task and were asked to have their hands in their lap while at rest. Participants were instructed before each trial to reach continuously between the two targets making contact with the fingertip. Participants were instructed to be as accurate to the center of the target and to perform the task as quickly as possible; no verbal encouragement was provided within the trial. Data were recorded for five consecutive reaching cycles after participants started reaching, and participants were not instructed to stop reaching until a short time period elapsed following the 5 complete cycles. Both the stroke-affected and less-affected sides were collected, and that order was randomized.

Arm kinematics were recorded at 100Hz with a 7 camera Vicon motion analysis system (Vicon, Centennial, CO, USA). Each target (0.10m in diameter) was instrumented with a pressure sensor to quantify target contact and were synchronized with the motion capture system. A custom UE marker set was utilized including: 9 torso markers, radial and ulnar styloid, hand, finger-tip, forearm, shoulder, elbow, and a cluster set (3 markers) on each upper-arm. Static calibration trials were collected for each side prior to the dynamic trials. Data were reconstructed and labeled in Nexus (Vicon, Centennial, CO, USA),

and processed in Visual3D (C-motion, Germantown, MD, USA). A low-pass fourth-order, zero-lag Butterworth filter was applied to kinematic data with a cutoff frequency of 7Hz. All ranges of motion/excursion were calculated as the difference in joint angles between contact with the distal target and proximal target. UE joint angles were calculated as follows: shoulder flexion (rotation of the upper-arm in relation to the thorax about the x-axis) and elbow extension (rotation of the lower-arm in relation to the upper-arm about the x-axis). Trunk contribution was calculated as anterior flexion, lateral flexion, and axial rotation. Trunk rotation was defined for each reaching side such that counter-clockwise rotation of the trunk when using the right side and clockwise rotation when using the left-side were considered positive. Lateral flexion was defined as positive when leaning away from the targets.

A number of spatiotemporal parameters were calculated. Reach and return movement times were determined as the time between consecutive target contacts. Movement velocities were calculated by determining the derivative of the wrist position marker in the sagittal plane. Peak velocities were determined as the peak reach and return velocity that occurred between consecutive target contacts. Velocity profiles of the wrist marker were plotted to determine smoothness of movement using zero velocity crossings and were determined separately for the reach and return phases. The lowest number of velocity crossings possible was 5 such that there was a bell shape velocity profile for each reaching cycle (one acceleration and deceleration phase). Variable error (a measure of accuracy at contact) was assessed from the spatial distribution of the

finger tip marker as it made contact in relation to the mean of the target contacts (40) using the following equation: $VE = \frac{1}{n}\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2 + (y_i - \bar{y})^2}$ where x_i and y_i are the coordinates of the finger tip marker as it made contact with the target, $\bar{x}$ and $\bar{y}$ are the averaged coordinates, and *n* is the number of reaching cycles.

Electromyography (EMG) to determine muscle activation patterns (MAP). EMG was recorded from a pair of electrodes (1cm in diameter, 2cm inter-electrode distance, Noraxon, Inc., Scottsdale, AZ) from the biceps brachii, triceps brachii, posterior deltoid, anterior deltoid, middle deltoid, and upper-trapezius muscles according to published guidelines (50). EMG data were collected through a Myosystem 1200 (Noraxon, Inc., Scottsdale, AZ) and synchronized with Vicon at a sampling rate of 2000Hz. Data were band-pass filtered (16-400Hz) and then full-wave rectified. A root mean square value (RMS) in a 4-time domain analysis of EMG was calculated such that the RMS amplitude of EMG for each muscle was determined for the acceleration and deceleration phases of the reach and return. This has been demonstrated as a method to quantify EMG amplitude given that a maximum voluntary isometric contraction may not be accurate in survivors of stroke (51). EMG data were checked for outliers and values were removed from the analysis that were below 0.001 millivolts or exceeded a value of 2 standard deviations above the mean.

Data analysis. Descriptive statistics included mean and standard deviations (SD) were reported in the text [standard error of the mean (SEM) in

figures]. The stroke-affected side was compared to the less-affected side through one-way repeated-measures analysis of variance (RMANOVA) for the segmental contribution to reach (side as a factor), two-way RMANOVA's for the spatiotemporal outcomes (2x2; side-by-reach/return phase), and the MAP (2X4; side-by-acceleration/deceleration per phase). A one-way repeated measure ANOVA was utilized as a post-hoc measure to investigate interaction effects for MAPs. Pearson-product moment correlations were calculated for the kinematic ROM variables, functional ability scores (FM, BBT, and reaching time), and two MAPs (anterior deltoid and triceps). Statistical significance was set at $p \leq 0.05$.

Results

Segmental contributions to reach. Figure 1.2. illustrates the segmental contribution to reaching and Table 1.2. includes individual data. Participants used significantly more anterior trunk flexion [12.2±6.0° vs. 3.2±3.2°, respectively; $F(1,15) = 33.9$, $p < .001$] and rotation [10.4±2.5° vs. 7.5±2.0°, respectively; $F(1,15) = 20.1$, $p < .001$] when reaching with the stroke-affected side compared to the less-affected side. Participants used significantly less shoulder flexion when reaching with their stroke-affected side compared to the less-affected side [37.8±13.2° vs. 57.1±11.9°, respectively; $F(1,15) = 18.2$, $p = .001$]. Elbow extension, when reaching with the stroke-affected side, was approximately half compared to reaching with the less-affected side representing a significant difference [24.3±16.8° vs. 54.3±8.7°, respectively; $F(1,15) = 54.5$, $p < .001$].

Spatiotemporal outcomes. Figure 1.3. (panels A and B, two representative participants) depicts differences in velocity profiles when comparing the stroke-affected side to the less-affected side. These differences include longer duration to achieve the 5 cycles of reaching in the stroke-affected side [$F(1,15) = 18.7$, $p = .001$], but there was no difference between the forward reach versus return phase [reach vs. return; $F(1,15) = 0.19$, $p = .67$]. The average forward-reaching duration was 1.4±0.7 seconds for the affected side compared to 0.8±0.3 seconds with the less-affected side. The return times were 1.4±0.8 seconds for the more-affected and 0.8±0.4 seconds for the less-affected side. Although there was no difference in peak velocities between sides [0.87±0.3m/s for the affected side compared to 0.97±0.3m/s; $F(1,15) = 3.6$, $p = .076$], the peak velocities were significantly greater during the reaching phase compared to the return phase when simultaneously comparing both sides [$F(1,15) = 6.05$, $p = .026$]. The smoothness of the velocity profile was significantly different when comparing the number of zero velocity crossings, with significantly more crossings when participants reached with their stroke-affected side (see panel C in Figure 1.3.; at least 5 zero-velocity crossings required to complete the task). These zero velocity crossings occurred when participants made contact with the targets and the additional crossings occurred when velocities fluctuated as participants reversed their reaching direction. The fluctuations at target contact were more prominent than the velocities remaining below a 5% peak velocity threshold which would indicate a subject was resting/dwelling on the target. As illustrated in figure 1.3., there was a negative correlation (R^2=-0.52) between degrees of

elbow extension generated and zero-velocity crossings when reaching with the stroke-affected side, i.e., less joint motion, the greater number of zero-velocity crossings. This relationship is similar to segmental contributions to reach (see Table 1.3). All subjects were able to make contact with the target with the fingertip and the variability in finger position at target contact was calculated as the variable error. Subjects were more variable when reaching with the stroke-affected arm and hand (proximal target 0.6±0.4 cm; distal target 0.5±0.3 cm) compared to the less-affected hand [proximal target 0.4±0.1 cm; distal target 0.3±0.2 cm; $F(1,15) = 15.8$, $p = .001$].

Muscle activation patterns. Muscle activity was determined during 4 time domains and calculated as the RMS during the acceleration and deceleration phases of the reach and return. Figure 1.4 illustrates representative MAPs for the biceps, triceps, anterior, middle, and posterior deltoid, and upper trapezius, and figure 1.5 represents averages for the stroke-affected and less-affected sides. Biceps muscle activity was significantly less in the stroke-affected side [$F(1,11) = 7.86$, $p = .017$]. Differences in muscle activity of the triceps depended on the phase of the reach [interaction, $F(3,42) = 3.8$, $p = .017$] with significantly less activity in the stroke-affected side during the deceleration phase of the return movement [$F(1,14) = 6.88$, $p = .02$]. There was significantly less activity in the stroke-affected side in the posterior deltoid [$F(1,14) = 6.1$, $p = .027$] which was most prominent during the during the return. There was a significant side-by-time interaction [$F(3,30) = 4.0$, $p = 0.017$] in the MAP of the anterior deltoid with significantly less activity in the stroke-affected side during acceleration and

deceleration of the reaching phase [F (1,10) =9.43, *p*=0.012 and F (1,11) = 6.23, *p*=0.03, respectively]. There was significantly less middle deltoid amplitude in the stroke-affected side [F (1,13) = 4.8, *p* =.048] in all phases of reach. Amplitude of contraction in the upper trapezius muscle did not differ significantly comparing sides [F (1,11) = 3.3, *p* =.11].

Correlations between functional ability scores of the stroke-affected side, segmental contributions to reach, and MAPs of two muscles are presented in Table 1.3. The average FM score was 51.5± 11.1, with a range of 28-63. Participants did not exhibit any proprioception deficits in shoulder and elbow of the stroke-affected arm (data not included in FM score). The average number of blocks transported during the BBT was 21.9±10.8, with a range of 4-44. The segmental contributions to reach (shoulder, elbow, and trunk ROM) were significantly correlated with the FM, BBT, and the overall reaching time during the kinematic task. Two muscles of interest (anterior deltoid and triceps) were significantly correlated with shoulder ROM and the BBT. Additionally, the anterior deltoid was significantly correlated with reaching time.

Discussion

This study established kinematic and spatiotemporal outcomes and muscle activation patterns of CR in survivors of stroke in a task requiring continuous shoulder flexion/elbow extension without trunk restraint. This study extends the work of Prange, Jannink, et al. (42) by investigating how survivors of stroke generate CR while determining the contribution of the trunk and

characterizing a number of spatiotemporal parameters. We expected that movements would not be as smooth and coordinated when reaching with the stroke-affected side compared to the less-affected side. Results indicated more trunk, and less shoulder flexion and elbow extension when reaching with the stroke-affected side. Participants with limited elbow extension on the stroke-affected side experienced the greatest degree of velocity profile irregularities. There was greater activation in the anterior deltoid during the reaching phase and posterior deltoid during the return phase when comparing less-affected and stroke-affected MAPs. The triceps and anterior deltoid may have a distinct role in CR and functional ability evidenced by correlations with the kinematic and functional measures. These findings have direct clinical implications by fostering a better understanding among clinicians how interventions may target specific impairments through the therapeutic use of CR tasks.

Our results highlight a number of interesting spatiotemporal characteristics of CR in stroke. Previous reports have suggested that survivors of stroke are unable to achieve similar peak velocities compared to neurologically intact controls when performing a discrete reaching task (31). Results from our study demonstrate that although movement durations were significantly longer in CR when reaching with the stroke-affected side compared to the less-affected side, the peak velocities were not different. This suggests that survivors of stroke maintain some ability to accelerate but are not able to maintain faster movement speeds due to longer acceleration/deceleration phases. Alternatively, the longer reaching durations could have resulted from dwell times on the targets (partially

observed in panel B of Figure 1.3). We do not feel target dwell times were a factor because the absolute velocities of participants with extended reaching durations fluctuated at the target contact rather than remaining below a threshold of 5% of the peak velocity for a period of time. More likely, participants experienced greater difficulty in the reversal of the hand at target contact which resulted in a greater number of zero velocity crossings when using the stroke-affected side. Although there were more zero-velocity crossing when reaching with the stroke-affected side, approximately 2/3 of the sample fell within a similar range as the less-affected side suggesting that the majority of participants could more easily generate CR. Continuous reaching may be related to functional return of elbow extension and shoulder flexion as a greater ability to generate elbow extension was correlated with fewer irregularities in the velocity profile (see Figure 1.3), and both elbow range of motion and anterior deltoid MAP in acceleration for reach were correlated with a functional measure (BBT).

The consistency of spatiotemporal results with previous reports suggest that the cyclic nature of the task provided an adequate reaching structure for investigating how these movements are characterized in the stroke-affected side. Trunk contributions to reaching through anterior flexion and rotation reported here are consistent with previous literature describing discrete reaching tasks, (30) yet the current study extends the work of Prange, Jannink, et al. (42) by precisely quantifying trunk motion during a cyclic task. Subjects had more rotation when using the stroke-affected side (greater ROM) suggesting that is a compensatory trunk strategy during CR. In addition to the trunk contributions to

reach, subjects used less shoulder flexion and elbow extension when reaching with the stroke-affected side. One challenge is to determine the specific impairment(s) causing these limitations. The traditional view of decreased ability to generate elbow extension was due to triceps weakness and possible impedance from antagonist hyperactivity of the biceps. We failed to detect hyper-activity of the antagonist muscle (biceps) during forward reach since the amount of biceps activity did not change over time and there was significantly less biceps activity on the stroke-affected side. Alternatively, triceps weakness or inability to generate triceps muscle activity may contribute to the altered segmental contributions. The only instance, however, of significantly less triceps activity in the stroke-affected side occurred during the deceleration phase of the return movement. Prange, Jannink, et al. (42) suggested that triceps activity in the stroke-affected side had very low levels of activity throughout the reaching task compared to other MAPs including posterior deltoid. In reference to the leading joint hypothesis put forth by Dounskaia (52), the low levels of triceps activity may result from the shoulder being the leading joint with relatively greater cyclic fluctuations for this type of task. Within this framework, triceps activity is an important consideration for reaching tasks because it must incorporate interaction torques that result from the shoulder. We found that the ability to generate triceps activity in the return significantly correlated with performance on the BBT (see Table 1.3) which is intriguing because the BBT requires cyclic arm movements and the ability to activate the triceps muscle activity would benefit returning the arm to the retrieval side after the block had been released. The

decreased ability to generate/utilize elbow extension also resulted in greater velocity profile irregularities. These finding supports the concept that the ability to generate elbow extension is an important factor of motor control and function post-stroke (53).

Although a single motor control theory or hypothesis has not prevailed, the relationships between kinematics and muscle activation are of interest for clinical researchers. As described above, the leading joint hypothesis can add to the explanation of the differences in MAPs between the shoulder and elbow musculature. In comparison, the referent configuration hypothesis can be used to describe the interactions between central, biomechanical, and afferent components (54). Muscle activation depends on the comparison of the actual configuration to the referent configuration, and the nervous system elicits movement by altering the referent configuration. In the context of the current study, the reversal in motion would occur because of a reversal in the referent configuration and muscle activation would result as a difference between the actual and referent configurations. The MAPs of the anterior deltoid and posterior deltoid did exhibit greater degrees of cyclic variations at the reversal of motion. This is consistent with previous studies (42, 55). Of clinical interest, the anterior deltoid MAP significantly correlated with the amount of shoulder flexion, performance on the BBT, and reaching time during the kinematic task (see Table 3). Functional ability and movement speed appear to be related to the ability to generate greater activity in the anterior deltoid. Future studies should systematically investigate these relationship through carefully designed

experiments and/or computer simulations. Potential experiments may include comparing muscle activation patterns generated in a computer simulation of forward reach compared to experimentally recorded values. Doing so may uncover potential avenues for intervention to alter MAPs through training or augmentative approaches such as electrical-stimulation.

Clinical Implications. The results of this study highlight two important clinical implications. First, the incorporation of CR tasks as screening measures may provide insight into the severity of the motor impairments following a stroke. The ability to generate CR requires constant and repetitive interaction between motor output, musculoskeletal system, and afferent feedback such that the demands are inherently different than a discrete reaching task. Better understanding the ability to generate continuous reach will allow for more targeted interventions to improve the potential to incorporate the stroke-affected arm and hand in daily life. For example, slow performance on a CR task may suggest that MAPs are not sufficient to generate movement and could be targeted in an intervention. Secondly, the results emphasize reaching characteristics that should be considered within structured interventions that utilize CR tasks. Many of the traditional and newer movement therapies tend not to include CR tasks which reduces the likelihood of integrating motor output with afferent feedback required for smooth coordinated movement. For example, traditional approaches like neuro-developmental treatment (NDT) emphasize stability and tone reduction through stretching and weight-bearing, whereas constraint-induced therapy often utilizes discrete movement tasks. A number of

interventions, however, have incorporated cyclic reaching for survivors of stroke (10, 56, 57). Our results provide evidence that subjects with mild to moderate impairments can accomplish CR without long dwelling periods at target contacts, yet used altered strategies when compared to the less-affected side. Interventions, therefore, may need to consider and target these specific motor impairments within interventions that incorporate CR.

Limitations

Participants presented with a level of motor function common in approximately 20% of the stroke population, (58) limiting the potential to generalize findings to survivors with severe motor deficits. One challenge in the field of stroke rehabilitation is the limited ability to characterize scapular movement with motion analysis. We minimized this limitation by characterizing the trunk contributions with greater specificity in relation to rotation, lateral flexion, and anterior flexion (30) and by incorporating MAP of the shoulder region.

Conclusions

Mild to moderate motor control impairments in survivors of stroke did not limit the ability to generate CR, yet there were distinct strategy differences between the stroke-affected and less-affected sides. Participants used more trunk rotation and had diminished MAP amplitudes in the proximal musculature (anterior and posterior deltoid) when comparing the stroke-affected to the less-affected side, yet these reductions were less prominent in the biceps and triceps.

The significant and moderately strong correlations linking functional to kinematic and MAP outcomes suggest that a CR task may be of benefit as a post-stroke screening measure to determine the ability to generate continuous movement of the stroke-affected UE. These findings suggest that additional research investigating cyclic vs. discrete reaching in survivors of stroke is warranted to aid in the refinement of UE interventions and/or updating the theoretical approaches to UE interventions.

Acknowledgments

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Table 1.1. Participant demographics.

Subject/Sex/Age	Time since stroke (years)	Stroke Type/ Side of stroke	Lesion location	FM	BBT
1/M/44	0.6	I/R	MCA	48	20
2/F/74	5	I/R	Frontal	50	14
3/F/66	6.8	H/L	MCA	57	28
4/M/61	1.3	I/O	pons, cerebellar	60	18
5/M/74	4	I/L	medulla	48	13
6/M//86	4.1	I/O	anterior, central pontine	47	28
7/M/68	1.6	I/L	MCA	60	22
8/F/75	3.1	I/R	parietal	57	25
9/M/63	13.8	I/L	MCA	28	4
10/F/41	0.5	I/R	MCA	60	19
11/F/65	1.8	H/L	cerebellar	56	18
12/M/81	1.3	I/O	pons	39	20
13/M/70	2.5	I/L	centrum semiovale	63	44
14/M/70	4.5	I/L	posterior parietal	61	30
15/F/64	3.5	I/L	corona radiata	61	41
16/F/64	3	I/R	basal ganglia	29	6
Average (range) 66.6±11.6 (41-86)	3.6±3.2 (0.5-14)			(28-63)	(4-44)
Counts 9 M; 7F		2 H; 14 I	8 L; 5 R; 2O		

Abbreviations: M = male; F = female; I = ischemic; H = hemorrhagic; L = left; R = Right; O = other; FM = Fugl-Meyer; BBT = box and block test; MCA = middle cerebral artery

Table 1.2. Kinematic data for reaching with the stroke affected side.

Subject	Trunk Flexion ROM (°)	Trunk Rotation ROM (°)	Shoulder Flexion ROM (°)	Elbow Extension ROM (°)	Reach Duration (sec)
1	7.5	11.1	36.5	31.4	0.9
2	14.7	12.6	31.5	4.8	2.5
3	9.2	10.1	33.4	23.5	0.8
4	3.2	6.4	49.4	39.1	0.9
5	18.2	10.2	20.6	-2.2*	2.2
6	16.1	6.9	34.8	17.9	1.6
7	15.4	9.1	26.3	20.7	1.5
8	15.0	13.5	28.5	28.8	1.3
9	20.0	10.7	15.7	-1.1*	1.6
10	7.2	13.1	49.0	50.9	1.0
11	17.0	13.1	39.2	20.6	3.0
12	8.2	10.7	39.9	20.7	1.3
13	16.7	8.4	40.8	21.7	0.6
14	2.3	6.0	67.7	51.2	0.9
15	4.7	10.1	56.5	48.7	0.8
16	19.6	14.1	34.2	12.3	2.0
Average (SD)	12.2 (6.0)	10.4 (2.5)	37.8 (13.2)	24.3 (16.9)	1.4 (0.7)

Abbreviations: ROM = range of motion

* ROM values negative because there was less elbow extension at the distal target relative to the proximal target indicating a slight flexion ROM.

Table 1.3. Correlations between kinematic, functional, and MAP outcomes.

Outcome	FM	BBT	Shoulder ROM	Elbow ROM	Trunk ROM	Ant Delt acc reach	Triceps dec return
Reaching Time	-0.60* (15)	-0.57* (15)	-0.49* (16)	-0.61* (16)	0.40 (16)	-0.58* (12)	-0.29 (15)
FM		0.71* (15)	0.54* (15)	0.68* (15)	-0.60* (15)	0.25 (11)	0.43 (15)
BBT			0.61* (15)	0.68* (15)	-0.62* (15)	0.55* (11)	0.57* (15)
Shoulder ROM				0.87* (16)	-0.81* (16)	0.55* (12)	0.56* (15)
Elbow ROM					-0.84* (16)	0.46 (12)	0.63* (15)
Trunk ROM						-0.29 (12)	-0.63* (15)
Ant Delt (acc reach)							0.42 (11)

(n) *$p<.05$

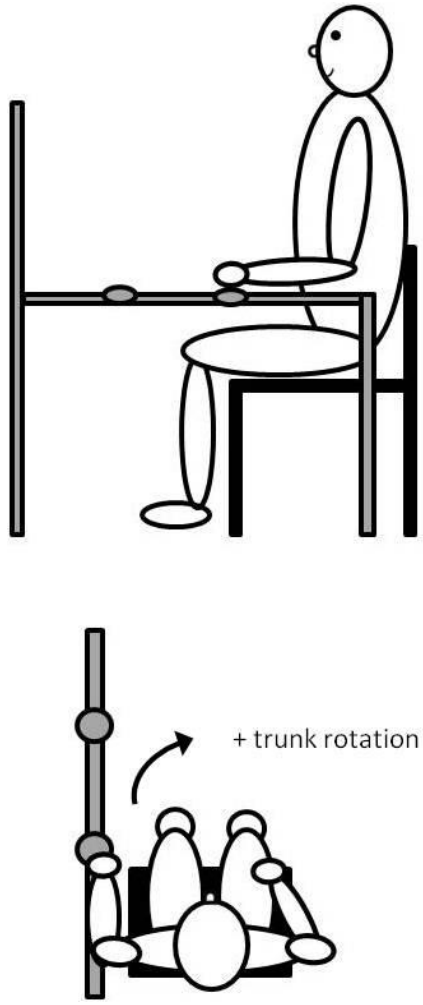

Figure 1.1. Schematic of experimental setup for the left side. Participants were instructed to reach back and forth between the two targets located in a para-sagittal plane at the height of 0.71m. The pressure-sensitive targets 0.10m in diameter were placed 0.35m apart and were synchronized with the motion capture system to record when contact was made with the target. Participants were instructed to reach as accurately and as quickly as possible. The trunk was not restrained during trials. Both the less-affected and the affected sides were collected and the target apparatus was transferred to the opposite side such that it was located in the parasagittal plane on the side being tested.

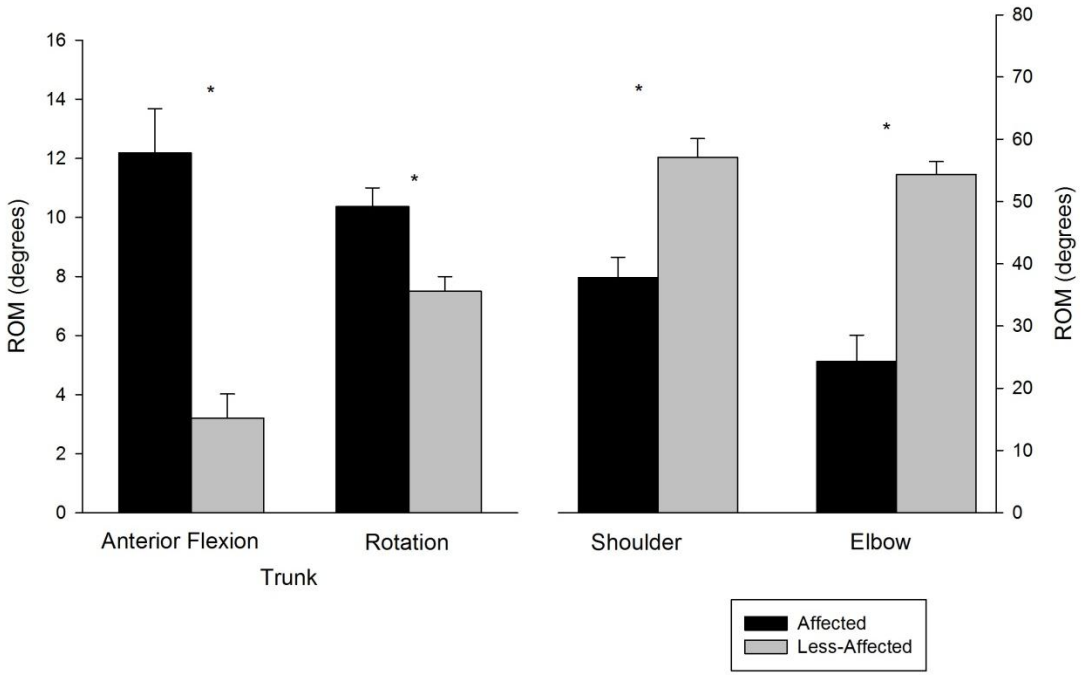

Figure 1.2. Segmental contribution to reach included range of motion (ROM) of trunk anterior flexion, trunk rotation, shoulder flexion and elbow extension. Subjects used significantly more anterior trunk flexion and rotation when reaching with the stroke affected side compared to the less-affected side. The reach from the proximal to distal target was accomplished with significantly less elbow extension and shoulder flexion when using the stroke-affected side. Data are plotted as means and error bars represent SEM (* $p < .05$).

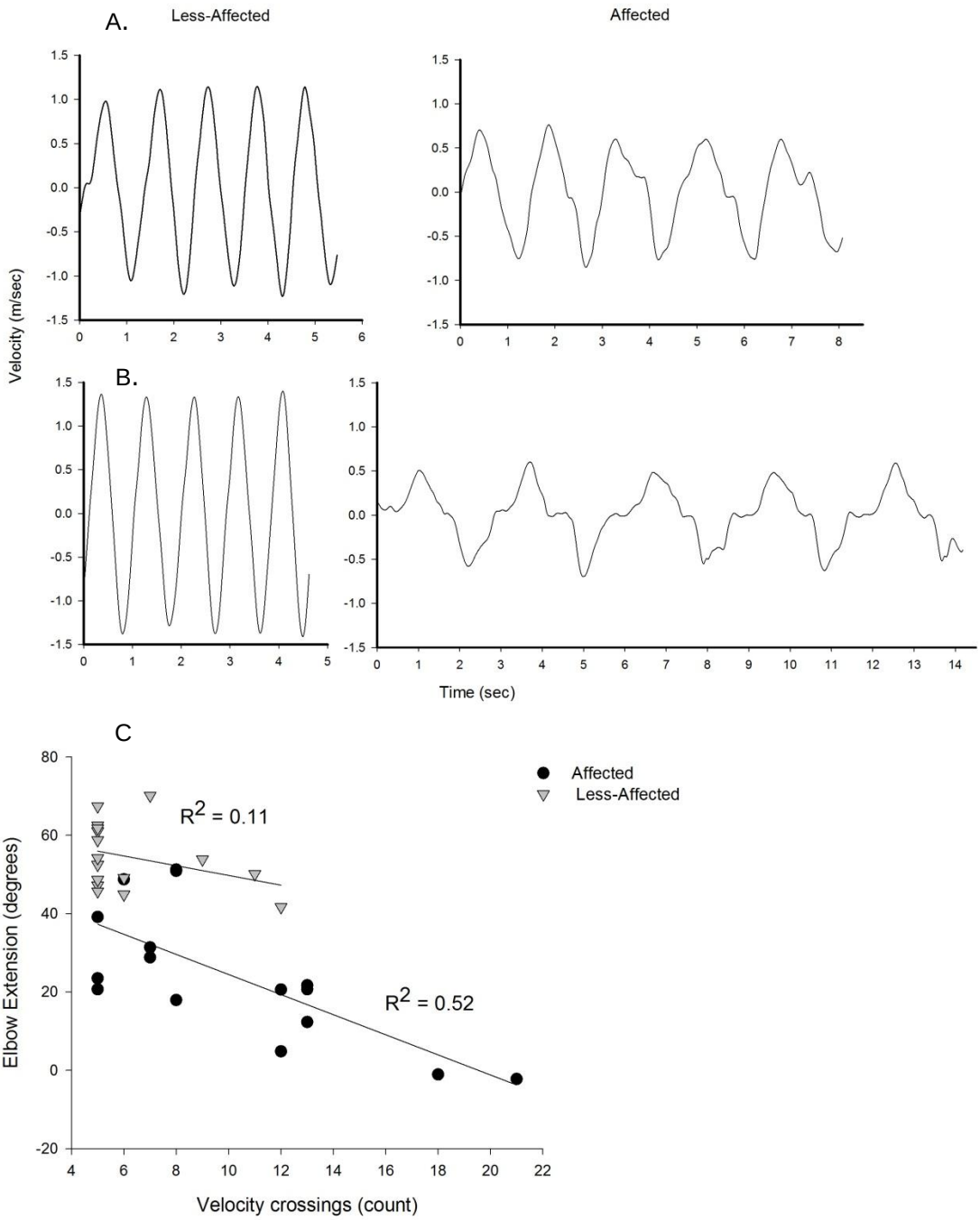

Figure 1.3. Spatiotemporal parameters of reach. Panels A and B illustrate wrist velocity profiles in two representative subjects when reaching with the less-affected stroke-affected sides. When comparing the stroke-affected side (right side of Panel A and B), the subject represented in Panel A had smoother

accelerations and decelerations around target contact (which would occur at zero velocity). The positive velocities represent the forward reaching phase and the negative represent the return phase. The stroke-affected side of Panel B represents a subject that was less-able to reverse motion smoothly at target contact illustrated by the brief zero velocity between the peaks in both positive and negative velocities. This subject also had lower peak velocities and required more time to complete the 5 reaching cycles. Panel C represents the relationship between the number of zero velocity crossings (a metric of movement smoothness) with the amount of elbow extension. Elbow extension accounts for approximately 50% of the variance in movement smoothness such that subjects with more elbow extension had smoother movements (R^2=0.52).

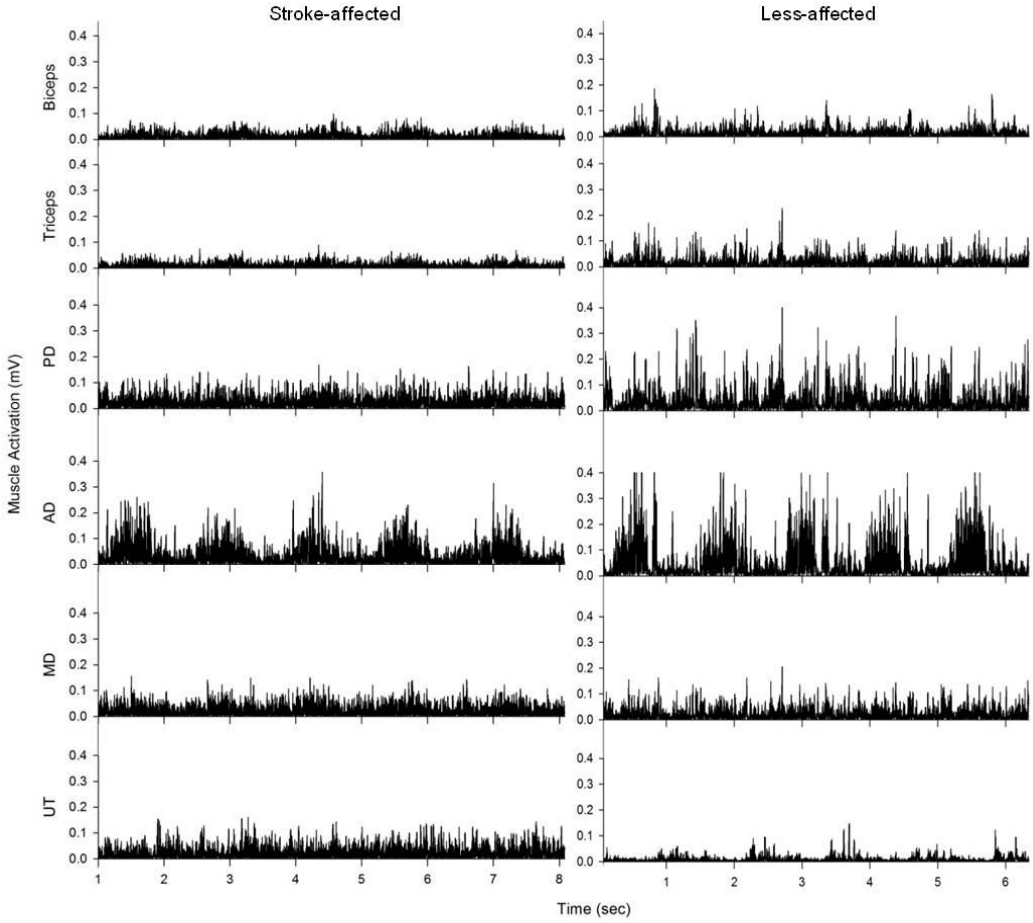

Figure 1.4. EMG recordings from a representative subject for both the stroke-affected and less-affected sides. Abbreviations: PD, posterior deltoid; AD, anterior deltoid; MD, middle deltoid; UT, upper trapezius.

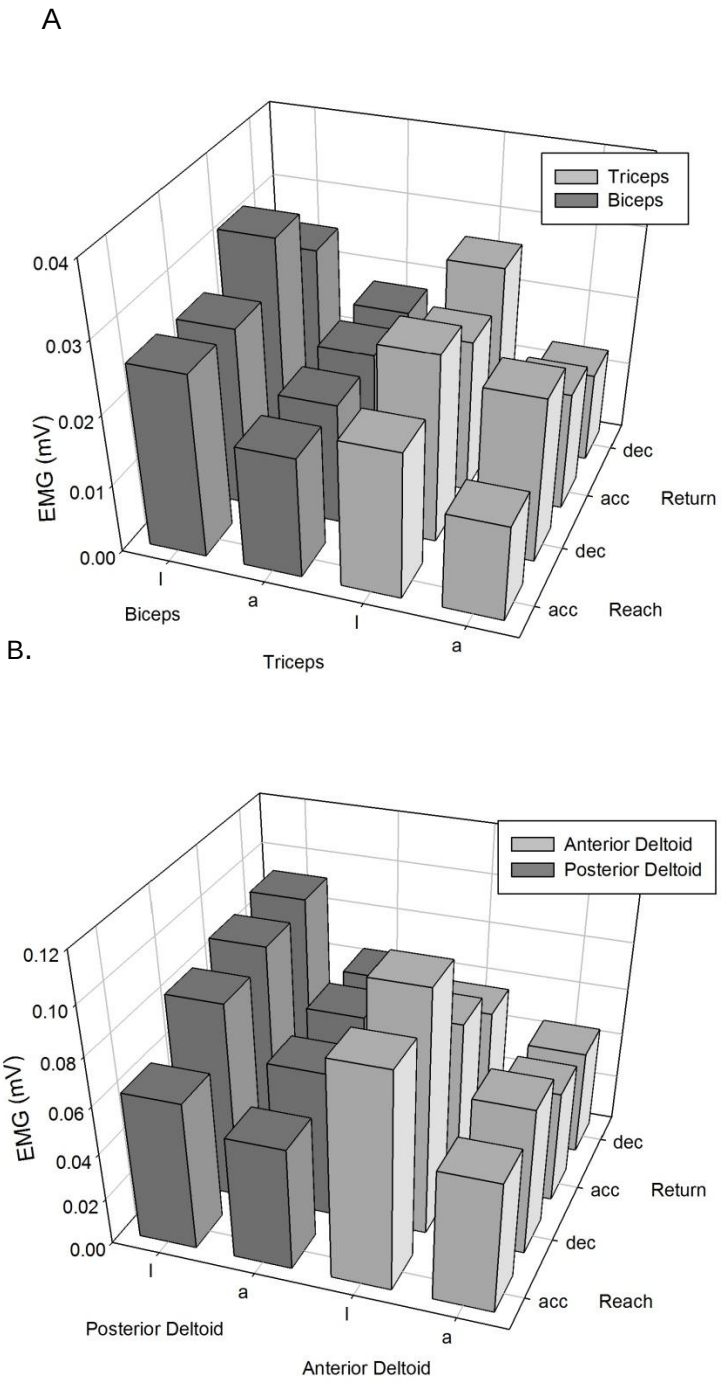

Figure 1.5. Muscle activation profiles during cyclic reaching. Panel A illustrates the MAP for the biceps and triceps during cyclic reaching for both the affected and less-affected side (acc=acceleration phase, dec=deceleration phase,

a=affected, l=less-affected). Panel B illustrates the same characteristics for the anterior deltoid and posterior deltoid muscles. The MAP of the more proximal muscles illustrate the potential contributions of these muscles to cyclic reaching such that the anterior deltoid had greater activation during the reaching phase whereas the posterior deltoid had greater activation during the return phase.

CHAPTER III – MANUSCRIPT II

Title: Cyclic versus discrete reaching in survivors of stroke

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Key Words: Stroke, reach, impairment, motor control, kinematic motion analysis, continuous, discrete
Tables: 2
Figures: 3

Manuscript Abstract

Background: Stroke rehabilitation programs often target compromised reaching with interventions using discrete and/or cyclic reaching tasks, yet no comparison exists between these two movements in survivors of stroke. Objective: To investigate kinematic differences in discrete and cyclic reaching in survivors of stroke, and determine relationships between kinematic outcomes and clinical assessments. Methods: Seventeen chronic stroke survivors completed functional testing (Fugl-meyer, FM; and Box and Block Test, BBT) and kinematic motion analysis of upper extremity reaching with the stroke-affected and less-affected side. Participants were instructed to reach between two targets either discretely or cyclically. Kinematic outcomes included shoulder, elbow, and trunk range of motion (ROM), movement time, peak velocity, variable error, and muscle activation patterns for the anterior deltoid, biceps and triceps. Results: Significantly less shoulder and elbow ROM, and significantly more anterior trunk ROM was used with the stroke-affected side compared to the less-affected side. Participants used significantly more trunk rotation during cyclic reaching with the stroke-affected side compared to discrete reaching. The peak velocity, variable error, and movement times were not different between discrete and cyclic reaching in the stroke-affected side. Kinematic variables had moderate to good correlations with the FM and BBT. Conclusions: Greater trunk rotation during cyclic reaching likely represents an additional compensatory strategy when using the stroke-affected side. Survivors of stroke were able to integrate afferent feedback with motor output when reaching with the stroke-affected side without

consequential effects on motor performance. This study highlights the potential to incorporate cyclic reaching in neurorehabilitation interventions and assessments.

Introduction

Reaching ability is often severely compromised following a stroke. Efforts to develop or refine efficacious upper extremity (UE) interventions rely on a thorough understanding of motor control impairments post-stroke. Intensive, structured interventions (8, 10) have demonstrated the potential to increase reaching ability (e.g., faster), however, understanding how the types of reaching tasks completed during the intervention impact motor control strategies is not clear. For example, reaching can be performed as a discrete or cyclic task, but little research exists in how these movements are performed by survivors of stroke. This is important because the motor control strategies may differ between the two tasks (35). Discrete movements, while bounded by stationary periods, may rely heavily on pre-programming such that a generalized motor program specifies the relative timing and force prior to the initiation of the movement. Cyclic reaching with its recurring patterns is more dependent upon continuous feedback requiring real-time, dynamic changes in motor programming and execution. Improving our understanding of how discrete and cyclic reaching tasks are performed by survivors of stroke will provide insight into if and how different motor control strategies are used. Such insights should influence how reaching tasks are used in UE stroke rehabilitation interventions.

A thorough description of discrete and cyclic reaching kinematics in survivors of stroke is important because UE interventions rely on these movements as a foundation for structured tasks. For example, a number of interventions predominately rely on discrete tasks, including constraint-induced

therapy (CIT) (8, 9). Although the quantification of reaching tasks within CIT is lacking, the majority of these tasks would be considered discrete (e.g. reaching to turn on a light switch or putting an item in cupboard). In contrast to interventions that use discrete reaching, interventions using cyclic reaching or movements include rhythmic auditory stimulation (RAS) (10, 59), bilateral arm training with rhythmic auditory cueing (BATRAC) (56), among others (57, 60). Previous research has shown that UE interventions influence movement strategies and/or compensatory movements (8, 10, 61). For example, we demonstrated a sustained reliance on compensatory trunk movement following CIT (8), whereas RAS reduced compensatory trunk movement (10). The differential effects suggest that response to interventions, in part, may vary depending on the task structure. Therefore, a direct comparison on cyclic versus discrete reaching to characterize the immediate response to such task demands is warranted to expand the evidence-base on which interventions are developed.

In addition to interventions that use different reaching paradigms, various screening/outcome measures used to determine recovery and/or efficacy of interventions also use discrete and cyclic tasks. The Wolf Motor Function Test (WMFT) utilizes discrete tasks to characterize functional capacity and motor performance (62). Examples of these tasks include placing the hand on a table, picking up a various objects including a paper clip, pencil, can, and making quick, ballistic movements independently for many of the degrees of freedom in the UE (e.g., elbow flexion/extension). The Fugl-Meyer assessment (FM) utilizes both discrete movements and a cyclic pointing task. This discrete movements are

used to evaluate motor function from a synergy framework and the cyclic, knee-to-nose task to assess speed of motion, tremor, and dysmetria (46). The Box and Block Test (BBT) is a measure of hand dexterity including grasping, transporting, and releasing small blocks as quickly as possible in a cyclic/repetitive fashion within 1-minute. The potential exists that discrete tasks evaluate performance differently compared to the cyclic tasks. The relationships between the clinical assessments and the kinematic outcomes will provide insight into which kinematic variables are related to clinical assessments. For example, is there a relationship between the degree of trunk rotation used during a reaching task with a clinical outcome that incorporates cyclic movement? Better understanding these relationships may reveal the importance of incorporating motion analysis as an outcome measure for stroke rehabilitation (2).

Previous research characterizing movement patterns in survivors of stroke have relied on discrete (29) or cyclic tasks (53), but no direct comparison of these tasks exist. This study, therefore, sought to characterize kinematic strategies in survivors of stroke during discrete and cyclic reaching tasks. We hypothesized that survivors of stroke would use more compensatory patterns (e.g., trunk flexion) and slower movements when reaching with the stroke-affected side compared to the less-affected side. We hypothesized that the movement patterns generated during cyclic reach would better correlate with clinical measures incorporating cyclic movement. Given the paucity of data for an unconstrained, forward reaching task, we explored the differences between discrete and cyclic reaching, using the less-affected side as a control. The results

of this study will provide clinical researchers with an evidence-base for the incorporation of discrete or cyclic tasks for reaching interventions, and provide insight into the different mechanisms that are assessed with outcome/screening measures.

Methods

Participants. Seventeen survivors of stroke [10 male; 9 left CVA; mean of 3.7 (SD ±3.1) years post-stroke] with a mean age of 65.6 (SD±11.9) years participated and provided written informed consent. All study procedures were approved by the local institutional review board. Table 2.1 summarizes participant demographics. Participants were at least 6 months post-stroke and had at least 10° of active wrist extension and approximately 30° of active shoulder flexion, both in the stroke-affected side. Participants were excluded if they had a Mini-Mental State Exam score less than 24 (45), had other neurologic conditions (e.g., multiple sclerosis, Parkinson's disease), or had injections to treat spasticity within 3 months of participation. These criteria are typical for subjects recruited for intensive therapeutic interventions. Participants completed two functional assessments of the stroke-affected side including the UE portion of the FM (46) and the BBT. These measures have known psychometric properties and have been evaluated as outcome measures for survivors of stroke (47-49).

Motion capture setup and outcomes. See Figure 2.1. for experimental setup. Participants reached between two targets as accurately and quickly as possible following 1–2 practice trials. Kinematic and electromyography (EMG)

data were recorded for both the stroke-affected and less-affected sides. Two reaching tasks were completed with the order randomized; five consecutive reaching cycles and 5 discrete trials. Participants were instructed to reach continuously between the two targets as fast as possible until instructed to stop. We made sure that at least 5 complete cycles were collected after movement was initiated prior to asking participants to relax and participants were not informed of the number of required reaching cycles. During the discrete trials, participants were instructed to start with their hand on the proximal target, reach forward as fast as possible following an auditory cue, and stop and maintain a resting position on the distal target. Arm kinematics were recorded at 100 Hz with a Vicon system (Centennial, CO) using a custom UE marker set and processed in Visual 3D^{TM} (C-motion). The locations of the UE marker set included C7, T10, sternal notch, 4 tracking markers on the back, a 3-marker cluster set on the upper-arm, forearm, styloid processes of the radius and ulna, head of 3rd metacarpal, and a marker on the dorsal side of the distal phalanx of the 2nd digit. Upper extremity joint angles were calculated as follows: shoulder flexion (rotation of the upper-arm in relation to the thorax about the medial-lateral (ML) axis), elbow extension (rotation of the lower-arm in relation to the upper-arm about ML axis), and trunk anterior flexion, lateral flexion, and axial rotation.

Shoulder, elbow, and trunk ranges of motion (ROM) were calculated as the difference in joint angles between target contacts. The targets were instrumented with pressure sensors; target contacts were defined as the decrease in pressure as the hand left the proximal target and by initial contact

(increase in pressure) with the distal target. Motor performance parameters included the average reach duration, average of the 5 peak velocities, and variable error (measure of accuracy at target contact). The derivative of the wrist position marker in the sagittal plane was used to determine the peak velocity between target contacts. Variable error was assessed from the spatial distribution of the fingertip marker as it made contact in relation to the mean of the target contacts (40) using the following equation:

$VE = \frac{1}{n}\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2 + (y_i - \bar{y})^2}$ where x_i and y_i are the coordinates of the fingertip marker as it made contact with the target, $\bar{x}$ and $\bar{y}$ are the averaged coordinates, and *n* is the number of reaching cycles. Electromyography (EMG) data were recorded from a pair of electrodes (1cm in diameter, 2cm inter-electrode distance, Noraxon, Inc., Scottsdale, AZ) from the anterior deltoid, biceps brachii, and triceps brachii muscles according to published guidelines (50) to determine muscle activation patterns (MAP). A root mean square value (RMS) in a 2-time domain analysis was calculated (acceleration and deceleration phase of the reach). The acceleration phase was defined as period from target contact to peak velocity and the deceleration from peak velocity to distal target contact. RMS is a method to quantify EMG amplitude given that a maximum voluntary isometric contraction may not be accurate in survivors of stroke (51). EMG data were checked for outliers and values were removed from the analysis that were below 0.001 millivolts or exceeded a value of 2 standard deviations above the mean.

Data analysis. Descriptive statistics including means and standard deviations (SD) are reported in the text [standard error of the mean (SEM) is reported in figures]. A repeated-measures analysis of variance (RMANOVA) was used for the segmental contribution to reach [2x2; side (stroke-affected, less-affected) x type (discrete, cyclic)], and the MAP (2x2x2; side-by-type-by-acceleration/deceleration). Statistical significance was set at $p < 0.05$. Post-hoc, paired samples *t*-tests were then used to determine differences between discrete and cyclic reaching within the stroke-affected and less-affected sides when there was a significant main effect for the type of reach or an interaction effect. A Bonferroni correction was applied with a resulting α of 0.025. Pearson-product moment correlations were used to explore relationships between the clinical assessments (FM and BBT) and kinematic variables (shoulder, elbow, and trunk ROM). The strength of the correlations were determined as follows: 0-0.25 little or no relationship; 0.25-0.5 fair relationship; 0.5-0.75 moderate to good relationship; and above 0.75 good to excellent relationship (63).

Results

Reaching Kinematics. Shoulder flexion, elbow extension, and trunk flexion/rotation ranges of motion are shown in Figure 2.2. Participants used significantly less shoulder flexion ROM when reaching with the stroke-affected side as compared to the less-affected side ($F=25.8$, $p < 0.001$). Shoulder flexion ROM was 41.1 (±11.3)° when reaching discretely with their stroke-affected arm and 37.0 (±13.1)° during the cyclic task. When reaching with the less-affected side, shoulder flexion ROM was 59.5 (±8.9)° during discrete and 56.9(±11.6)°

during cyclic reaching. A main effect for type of reach was observed (F=8.0, p = 0.01) with greater shoulder flexion ROM associated with discrete reach.

Similar to shoulder flexion, participants had significantly less elbow extension ROM when reaching with stroke-affected side compared to the less-affected side (F=70.6, $p < 0.001$). Mean elbow extension ROM was 26.1(±17.1)° during discrete reaching with the stroke-affected arm and 23.1(±17.0)° during cyclic reaching. When reaching with the less-affected side, participants used 60.3 (±11.1)° during discrete and 54.0 (±8.3)° during cyclic. There was a significant main effect for type of task (F=11.1, p = 0.004); the post-hoc test for the stroke-affected was not significant (t = -1.2, p = 0.23), but there was a significant difference when using the less-affected side (t = -3.7, p = 0.002).

Participants used significantly greater trunk flexion ROM when using the stroke-affected side compared to the less-affected side, but the trunk flexion ROM did not differ between the cyclic and discrete reaches (F=58.9, $p < 0.001$, F=0.8, p = 0.4, respectively). A significant interaction was observed in the degree of trunk rotation ROM (F=8.2, p = 0.01). Post-hoc analyses determined significantly more trunk rotation when reaching cyclically with the stroke-affected side (t = 2.9, p = 0.011), but no differences in task when using the less-affected side (t = 0.2, p = 0.8).

Motor performance was generally slower when using the stroke-affected side, yet variability at target contacts was not different between sides. There was a significant interaction in the peak velocities of the hand between the side and

type of reach (F=13.8, p = 0.002). The slowest peak velocity was recorded during discrete reaching with the stroke-affected side (0.7 ± 0.3 m/s). During cycling reaching with the stroke-affected side, peak hand velocity was 0.9 m/s (±0.3), but this was not significantly faster than the discrete reaching (t = 1.7, p = 0.1). Participants reached faster with the less-affected side, achieving peak velocities of 1.1 ± 0.3 m/s for discrete and 1.0 ± 0.3 m/s for cyclic reaching. There was a main effect for side considering time to complete a reach with significantly slower reaching using the stroke-affected side compared to the less-affected side (F=25.4, p < 0.001), but no main effect in reaching time for type of reach. The average time to complete a reach was 1.1 ± 0.5 seconds for the stroke-affected side (both discrete and cyclic) and 0.69 ± 0.3 seconds and 0.66 ± 0.3 seconds for the less-affected side (discrete and cyclic, respectively). The error at target contact was not significantly different (p > 0.05) between the stroke-affected and less-affected side and the type of reach performed (0.5cm cyclic and 0.4cm discrete for stroke-affected and 0.3 cm cyclic and 0.4 cm discrete for less-affected).

EMG. Muscle activation patterns for the anterior deltoid, biceps, and triceps muscles are illustrated in Figure 2.3. Participants generated significantly less muscle activity in the anterior deltoid reaching with the stroke-affected side compared to the less-affected side (F = -8.4, p = 0.01). No differences were observed between sides or between the type of reach for either the biceps (F = 4.5, p = 0.05 and F = 2.2, p = 0.1, respectively) or triceps (F=0.72, p = 0.4 and F=0.05, p =0.8, respectively).

Relationships between clinical assessment and kinematic outcomes. The mean FM scores were 51 (±11.0) out of 66 for the UE portion of the FM, with a range of 28 to 63. Mean BBT scores were 20.9 (±11.2) and ranged from 4 to 44. The correlations between the functional and kinematic measures of the stroke-affected side are presented in Table 2.2. The functional outcomes were significantly positively correlated with shoulder flexion and elbow extension ROM for both cyclic and discrete tasks. Additionally, the amount of trunk flexion and rotation used during cyclic reaching were significantly negatively correlated with BBT scores. A number of significant correlations were observed between the kinematic variables during the discrete and cyclic reaching tasks including shoulder flexion (positively correlated with elbow extension, negatively correlated with trunk flexion and rotation), elbow extension (negatively correlated with trunk flexion), and trunk flexion (positive with trunk rotation in cyclic reaching); yet no significant correlations between the degree of trunk rotation and any of the cyclic variables during the discrete task.

Discussion

A number of important findings support the previously stated hypotheses. First, the results of this study highlight movement strategy differences between the stroke-affected and less-affected sides including larger compensatory movements during stroke-affected reach. This study also explored the differences in cyclic and discrete reaching in survivors of stroke. Our results suggest that the motor control strategy shifts proximally when sustained, cyclic reaching movements must be generated. In the stroke-affected side, there was

significantly more trunk rotation when reaching cyclically. Second, no differences between the type of reach (discrete vs. cyclic) in motor performance (reaching time or variability at target contact) suggested that survivors of stroke were able to integrate afferent feedback with motor output when reaching with the stroke-affected side without detrimental effects on motor performance. Third, the shoulder and elbow ranges of motion during the two tasks (discrete and cyclic) were closely related (i.e., moderate to good correlations) with common clinical assessments, yet the degree of trunk rotation during cyclic reaching was negatively correlated only with a clinical assessment that incorporated cyclic motion. Collectively, these findings have a number of important clinical applications and implications for future research.

The finding that survivors of stroke use more trunk flexion when reaching forward was not surprising, but the recent advancements in kinematic motion analysis processing have facilitated a more comprehensive quantification of trunk movement (30) which we have used in this current study. A clear strategic use of trunk rotation during the cyclic tasks implies that survivors of stroke rely more heavily on a proximal control strategy when cyclic motion must be sustained with the stroke-affected side. Although trunk flexion has been considered as a compensatory movement, the degree of trunk rotation has received less attention (30). All of the other kinematic variables (shoulder flexion, elbow extension, and trunk flexion) had significant main effects for side. This suggests that when reaching with the stroke-affected side participants reached with less shoulder flexion and elbow extension and more trunk flexion compared to when reaching

with the less-affected side. Our EMG data support the inference that deficits in the upper arm and shoulder girdle contribute to altered kinematic strategies. Muscle activity in the anterior deltoid muscle was significantly less in the stroke-affected side compared to the less-affected side. This weakness or inability to generate muscle activity of the anterior deltoid may contribute to the increased reliance on trunk movement. Additionally, we did not observe differences between the stroke-affected and less-affected sides in muscle activity patterns of the biceps and triceps.

Previous reports of the advantages of cyclic movements over discrete include faster movements, but these studies often limit the number of degrees of freedom incorporated into the task (40), thus limiting the comparisons to the current study. Although reaching was generally slower in the stroke-affected side, there were no differences between the discrete and cyclic reaching. The variability at target contact was also not different between sides or between discrete and cyclic reaching. Our findings suggest that survivors of stroke are able to generate continuous motion without consequential effects on motor performance when comparing movement time, peak velocity, and variability at target contact in the stroke-affected side. We feel these are important outcomes because they highlight the ability for survivors of stroke to respond to and integrate afferent feedback while making real-time adjustments in the efferent/motor output to accomplish cyclic reaching. The results of this study provide the detailed description of how discrete movements are different than cyclic movements. This is an area for continued research because complex

interventions such as CIT or RAS are dependent on reaching tasks to elicit movement capacity changes. We have previously demonstrated the potential to incorporate a cyclic reaching task as a structured intervention to improve movement patterns and functional ability (10). The differences between reaching tasks should be taken into consideration when implementing a clinical intervention because discrete and cyclic reaching are often not explicitly considered in clinical practice. The attention to varying therapeutic tasks and interventions based on specific motor control demands may provide additional benefits in training UE movements. For example, incorporating cyclic reaching into structured interventions provides learning opportunities to use feedback during performance as repetitions are completed and perhaps facilitate better quality of motion and functional ability. The motor control strategy shifted more proximally during cyclic reaching (e.g., more trunk rotation), and that shift may serve as a foundation for improvements in functional ability when cyclic tasks are implemented during UE interventions.

A recent trend in stroke-rehabilitation literature has utilized kinematic motion analysis to provide a more quantitative description of movement strategy changes before and after interventions (2, 8, 10, 61). On-going research efforts in this area continue to clarify the relationships between kinematic motion analysis outcomes with clinical outcomes (29, 53). The clinical outcome measures in this study were most strongly correlated with the amount of shoulder flexion and elbow extension during both tasks. This may reflect the emphasis on these joints during clinical assessments such as the FM. Interestingly, the trunk movements

during the cyclic task were significantly and negatively correlated with the BBT scores suggesting that impaired use of the stroke-affected side (indicated by lower BBT scores) is associated with greater compensatory trunk flexion and rotation. All but one of the kinematic measures (shoulder flexion, elbow extension, and trunk flexion) were significantly correlated in the cyclic task. This was true to a lesser extent in the discrete task (see Table 2.2), and the degree of trunk rotation was not significantly correlated with any other kinematic measures in the discrete task. This further supports the finding of a distinct control strategy for cyclic reaching compared to discrete reaching in survivors of stroke using the stroke-affected arm and hand. The relationships between kinematic and clinical outcomes suggest that incorporating cyclic tasks as outcome measures for stroke rehabilitation is warranted. Quantifying movement strategies during continuous, cyclic reaching characterized the unique trunk involvement related to the clinical assessments that was not observed during the discrete task. Although kinematic motion analysis is not readily in all clinics, incorporating a cyclic functional task may provide insight into how movements are generated based on the relationships between the kinematic and functional/clinical assessments.

Implications and conclusions. There are a number of important clinical implications and future research directions from the findings from this study. The potential to incorporate cyclic reaching tasks into interventions is warranted to provide the opportunity to continuously integrate afferent feedback with efferent, motor output. The kinematic strategies between cyclic and discrete reaching were similar except for an increased reliance on trunk rotation, and there was no

tradeoff in motor performance. The degree of trunk rotation was not significantly different between the stroke-affected and less-affected side, suggesting that the increased reliance on trunk rotation during cyclic reaching with the stroke-affected side may not be detrimental. One question that remains unanswered in stroke rehabilitation is the long-term effects of continued compensatory strategies, i.e., secondary musculoskeletal problems. Advancements in kinematic motion analysis technology should facilitate the clinical use of kinematic outcome measures for stroke rehabilitation to assist in addressing this important clinical question. Research advances should also address the difficulty in quantifying scapular kinematics/function and how that influences the ability to reach. This will likely require additional imaging techniques (e.g., bi-planar fluoroscopy) to enhance the ability to detect movement of the scapula in relation to the humerus and thorax. Scapular impairments are well-known clinically, yet few options exist to precisely quantify scapular motion (64, 65). Similar to the processing advancements to better quantify trunk movement, a better understanding of scapular kinematics will provide a more complete understanding of the motor impairments post-stroke. We elected to track trunk rotation on markers independent of the shoulder girdle to minimize the influence of scapular motion on trunk measures, e.g., limiting the potential of shoulder protraction/retraction to be observed as trunk rotation. We felt this was an important consideration because of the current limitations to accurately measure scapular motions. This is an area for future research because our EMG data suggest that some of the impairment may originate in the shoulder girdle, i.e.,

weak anterior deltoid. Additionally, advancements in musculoskeletal modeling may contribute to a more complete interpretation of EMG data. The implications from this study certainly highlight the continued requirement for precise quantification of motor control strategies following a stroke.

We observed a distinct strategic difference when survivors of stroke were instructed to reach cyclically between two targets compared to discrete reaching such that there was a greater degree of trunk rotation. The increased demands for continuous motion altered trunk rotation, yet no differences were observed in motor performance (variability at target contact, reaching duration). These clinically relevant findings suggest that survivors are able to integrate afferent feedback with updated motor output by altering the kinematic strategy without a subsequent decrease in motor performance. This is an important finding for interventions because it suggests that participants can respond to continuous motor tasks.

Acknowledgment

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Table 2.1. Participant demographics

Subject	Sex	Age	Years post-stroke	Stroke Hemisphere	Type of Stroke
1	M	44	0.6	Right	Ischemic
2	F	74	5	Right	Ischemic
3	F	66	6.8	Left	Hemorrhagic
4	M	61	1.3	other	Ischemic
5	M	74	4	other	Ischemic
6	M	86	4.1	Right	Ischemic
7	M	63	13.8	Left	Ischemic
8	M	68	1.6	Left	Ischemic
9	F	65	1.8	Left	Hemorrhagic
10	F	75	3.1	Right	Ischemic
11	F	41	0.5	Right	Ischemic
12	M	81	1.3	Left	Ischemic
13	M	51	4.5	Left	Ischemic
14	F	63	3	Right	Ischemic
15	M	70	4.7	Left	Ischemic
16	F	64	3.7	Left	Ischemic
17	M	70	2.7	Left	Ischemic
Count:	10M; 7F		9Left; 6 Right	2 Hemorrhagic; 15 Ischemic; 2 others	
Average (SD)		65.6 (11.9)	3.7(3.1)		
Range:		41-86	0.5-13.8		

Table 2.2. Correlations between functional and kinematic measures.

Outcome	Functional	Cyclic					Discrete				
	BBT	Reach Time (sec)	Shoulder ROM	Elbow ROM	Trunk Flexion ROM	Trunk Rotation ROM	Reach Time (sec)	Shoulder ROM	Elbow ROM	Trunk Flexion ROM	Trunk Rotation ROM
Functional											
FM	**0.7**	-0.3	**0.6**	**0.7**	**-0.6**	-0.4	**-0.5**	**0.6**	**0.6**	-0.3	-0.4
BBT		**-0.5**	**0.6**	**0.6**	**-0.4**	**-0.5**	**-0.5**	**0.7**	**0.6**	-0.4	-0.4
Cyclic											
Reach Time (sec)			**-0.5**	**-0.6**	**0.6**	0.3	**0.8**	**-0.4**	**-0.5**	**0.5**	0.1
Shoulder ROM				**0.9**	**-0.8**	**-0.4**	-0.3	**0.8**	**0.8**	**-0.6**	0.04
Elbow ROM					**-0.8**	-0.3	**-0.5**	**0.7**	**0.8**	**-0.6**	-0.1
Trunk Flexion ROM						**0.4**	**0.5**	**-0.6**	**-0.7**	**0.7**	0.2
Discrete											
Reach Time (sec)								-0.2	-0.4	0.4	0.3
Shoulder ROM									**0.9**	**-0.6**	-0.2
Elbow ROM										**-0.8**	-0.2
Trunk Flexion ROM											0.2

ROM: range of motion; FM: Fugl-Meyer; BBT: Box and Block Test
Bold denotes significant $p<0.05$

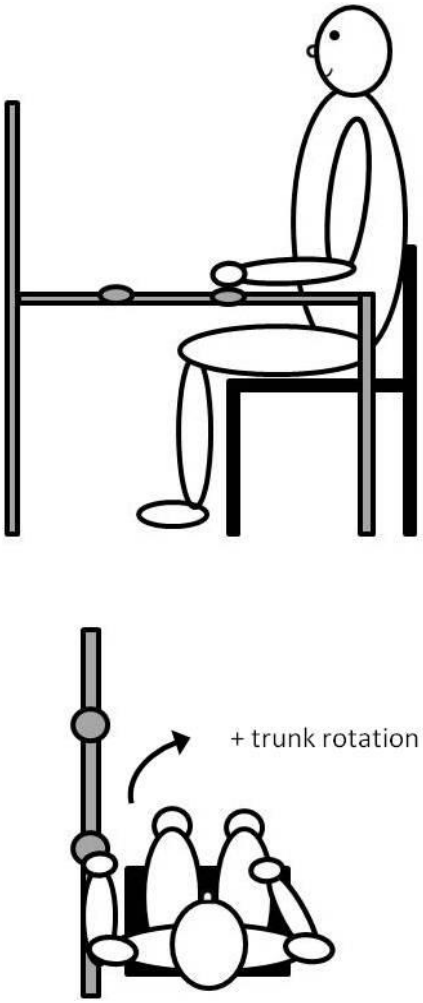

Figure 2.1. Schematic of experimental setup for the left side. Participants were instructed to reach back and forth between the two targets located in a para-sagittal plane at the height of 0.71m. The pressure-sensitive targets 0.10m in diameter were placed 0.35m apart and were synchronized with the motion capture system to record when contact was made with the target. Participants were instructed to reach as accurately and as quickly as possible. The trunk was not restrained during trials. Both the less-affected and the affected sides were collected and the target apparatus was transferred to the opposite side such that it was located in the para-sagittal plane on the side being tested.

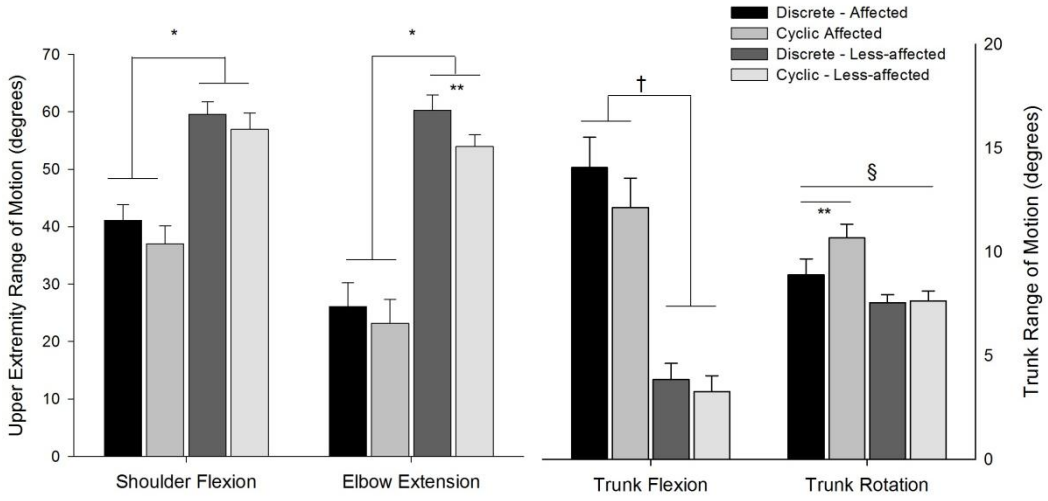

Figure 2.2. Range of motion for shoulder flexion, elbow extension, trunk flexion, and trunk rotation as participants reached from the proximal target to the distal target. * denotes a significant difference between sides (stroke-affected and less-affected) and a significant difference between reaching tasks (discrete and cyclic), † denotes a significant difference between sides, § denotes a significant interaction between side and task, and ** denotes a significant difference within the side for the type of reaching task (post-hoc analysis).

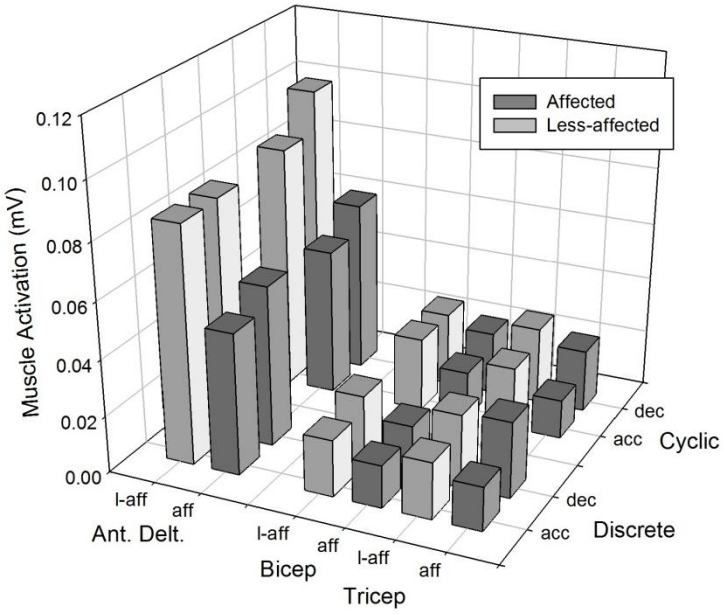

Figure 2.3. Muscle activation patterns for the anterior deltoid (ant delt.), bicep, and tricep when reaching with the stroke-affected and less-affected side separated by the acceleration (acc) and deceleration (dec) phase during discrete and cyclic reaching. Significantly less anterior deltoid activity was generated when reaching with the stroke-affected arm. No differences were observed in the biceps and triceps muscles.

CHAPTER IV – MANUSCRIPT III

Title: Functional repetitive transcranial magnetic stimulation increases motor cortex excitability in survivors of stroke

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Running title: Functional-rTMS in stroke

Manuscript Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) applied to the motor cortex with simultaneous voluntary muscle activation, termed functional-rTMS, may enhance use-dependent plasticity. The therapeutic potential of functional-rTMS requires more detailed characterization of the underlying neurophysiological mechanisms. Objective/Hypothesis: A single session of functional-rTMS will increase motor output and intracortical facilitation (ICF) to a greater extent than passive-rTMS (e.g., rTMS with no EMG triggering). Methods: Eighteen chronic stroke survivors were randomized into functional-rTMS (EMG-triggered rTMS) or passive-rTMS (rTMS only; control) conditions. Maximum voluntary contraction (MVC) force, force steadiness (coefficient of variation, CV) at 10% MVC, pinch task muscle activity, and intracortical inhibition (ICI) and ICF measures were assessed before and after rTMS. Functional-rTMS required subjects to generate muscle activity above a threshold during a pinch task to trigger each rTMS train; the passive-rTMS group received rTMS while relaxed. Results: Significant interactions (time x condition) were observed for the CV of force, abductor pollicis brevis (APB) muscle activity, APB ICI, and APB ICF. Passive-rTMS resulted in less APB activity after stimulation ($p<0.01$) and a decrease in CV of force ($p = 0.04$). Functional-rTMS decreased APB ICI and increased ICF ($p=0.05$ and 0.03, respectively) after stimulation. No significant changes were observed in FDI measures (EMG, ICF, ICI). Conclusion(s): Passive stimulation significantly reduced APB muscle activity during a steadiness task, while functional-rTMS modulated intracortical inhibition and facilitation for

the APB muscle. This study provides initial evidence that functional-rTMS may selectively modulate agonist muscle activity via disinhibtion and facilitation of the motor cortex.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) has the potential for therapeutic benefit during post-stroke rehabilitation (3, 66, 67). Neurologic damage from stroke often reduces primary motor cortex (M1) excitability (68), resulting in a net loss of descending excitatory input to spinal motor neurons. This neurologic origin is the dominant source of muscle weakness (43, 69, 70), and ultimately leads to upper extremity impairment. Animal and human studies have revealed the potential for undamaged adjacent regions of the cortex to contribute to recovery by functionally remodeling motor cortex representations (12-16). rTMS presumably modulates neural excitability of regions through its action on undamaged intracortical connections (19). Post-stroke motor behavior, therefore, is a primary target for rTMS interventions (71). Initial evidence suggests that active engagement or simultaneous motor training during rTMS may enhance cortical stimulation by promoting use-dependent plasticity (22-24). Full realization of the therapeutic potential of this approach requires further identification of neurophysiologic mechanisms including changes in the ability to generate and modulate muscle activity (72).

Many early protocols employed a passive rTMS protocol (no active engagement by the participant during stimulation) to modulate brain excitability in both neurologically intact and stroke populations. For example, in a healthy population, 20 seconds of high frequency (5Hz bursts of 3 pulses) rTMS to the hand area of primary motor cortex (M1) increased maximal grip force to a greater extent than sham stimulation or rest (73). In survivors of stroke, Kim et al. (74)

demonstrated that a single session of rTMS (20 stimuli at 80% of MT at 10Hz for 8 trains) increased motor cortex excitability and enhanced motor accuracy during a sequential finger tapping task. Yozbatiran et al. (75) demonstrated that 20 minutes of high-frequency rTMS (20Hz, subthreshold) in 12 participants favorably impacted motor performance. Studies have also examined the effects of multiple sessions of high-frequency rTMS as an intervention for survivors of stroke (24, 76, 77). Khedr et al.(76) demonstrated that rTMS combined with standard rehabilitation produced greater motor evoked potentials (MEP) and improved clinical outcomes. The impact of high-frequency rTMS on motor cortex excitability has been shown to be related to greater functional gains in survivors of stroke (78). These protocols required no active involvement of the subject during the stimulation, yet still provide evidence that fine motor control improves following high frequency rTMS delivered to the motor cortex.

The use of motor training and simultaneous cortical stimulation (defined here as functional-rTMS) is supported both theoretically (11, 12, 79) and with initial empirical evidence (22-24). Functional-rTMS may enhance the degree of use-dependent plasticity by augmenting the excitability of the motor circuits already engaged during a voluntary motor task. This represents a potential advantage of functional-rTMS over passive-rTMS. For example, Butefisch et al. (22) demonstrated that motor cortex rTMS paired with a motor training task enhanced motor memory in neurologically intact subjects. When coupled with muscle contractions, rTMS has been observed to facilitate agonist muscles but not antagonists in neurologically intact populations (23). Izumi and colleagues

(24) delivered TMS synchronized with maximal effort at hand opening in survivors of stroke and demonstrated a reduction in spasticity of the forearm flexors or improved manual performance. These promising initial reports suggest the need to determine the full therapeutic potential for functional-rTMS in survivors of stroke.

Functional-rTMS may improve recovery from stroke by enhancing use-dependent plasticity. This study sought to determine the impact of a single session of functional-rTMS on the excitability of the motor cortex and the corresponding motor output that may contribute to post-stimulation changes in motor behavior. We hypothesized that functional-rTMS would have an excitatory effect on the motor cortex. Given that optimal control of force may be an important neuromotor outcome because it is critical for upper extremity function in survivors of stroke (80, 81), we evaluated force steadiness and muscle activity during a lateral pinch task in parallel with neurophysiologic measures of intracortical inhibition (ICI) and intracortical facilitation (ICF).

Methods

Participants

Eighteen survivors of stroke (7 women, 11 men) volunteered and provided written informed consent (Table 3.1. for demographics). They were 64 ± 11 years of age (range 41-86 yrs) and 3.6 ± 3 yrs post-stroke (range 0.5 – 14 years). All study procedures were approved by the Human Subjects Committee of Colorado State University. Participants were screened for eligibility with a health

history questionnaire, Mini Mental Status Exam (45), an evaluation of movement (see inclusion criteria), and an electroencephalogram (EEG) assessed by a neurologist to rule out evidence of epileptiform activity. Participants met these inclusion criteria, 1) unilateral clinical stroke presentation at least 6 months prior to the study, 2) ability to actively flex the shoulder approximately 30 degrees, extend wrist and fingers, and achieve a lateral/key pinch, 3) a score of 24 or higher on the Mini Mental State Exam (45), and 4) the ability to actively participate for approximately 2 hours during the experimental sessions. Exclusion criteria were 1) medications that may lower seizure threshold, 2) history of epilepsy or seizure disorder, mass brain lesions, or epileptiform activity on screening EEG, 3) pacemaker or medication pump, metal plate in skull, metal objects in the eye or skull, or intracardiac lines, 4) history of heart disease, 5) pregnancy, 6) younger than 21 years.

Participants completed clinical assessments to determine level of impairment and functional ability. The Fugl-Meyer Motor Assessment (FM) is a stroke-specific, performance-based impairment index with well-characterized psychometric properties (45, 47). It is used to assess recovery of sensorimotor function including proprioception, movement, coordination, and reflex action of the shoulder, elbow, forearm, wrist, and hand. Scoring of each item is on a 3-point ordinal scale (0=cannot perform, 1=performs partially, 2=performs fully) (82). The Box and Block Test (BBT) measures the number of small blocks grasped, transported, and released in one minute, and has been evaluated as an outcome measure for survivors of stroke (48, 49).

Experimental setup.

Following the functional assessments, subjects were seated in a semi-reclined chair with the hemiparetic arm resting on a lap pillow. Generally, this resting position required internal shoulder rotation, elbow flexion, neutral forearm, and a slightly extended wrist. The skin was abraded and cleaned prior to the application of a pair of 8 mm surface electrodes (In Vivo Metric) in a belly-tendon arrangement on first dorsal interosseous (FDI), abductor pollicis brevis (APB), flexor pollicis brevis (FPB), and biceps brachii muscles. The electromyogram (EMG) from the FDI and APB was analyzed for the outcome measures. All EMG channels were monitored during the rTMS for safety considerations and the FDI, APB, and FPB were used to trigger the rTMS during functional-rTMS (see below). The EMG was recorded using a PowerLab 16/30 system (sampled at 2kHz; bandpass filtered at 10Hz-5kHz for the steadiness task and 1Hz-5kHz for the TMS outcomes). Figure 3.1. displays a schematic of the protocol.

Evaluation of motor function.

Evaluation consisted of maximum voluntary contractions (MVC) and force steadiness during a lateral pinch task. Participants were instructed to maintain a lateral pinch on a force transducer (Transducer Techniques MLP 100 for MVC task; MLP 10 for steadiness task) between the pad of the thumb and the proximal interphalangeal joint of the 1st digit. During MVCs, subjects were instructed to increase isometric force over approximately 3 seconds and then exert maximal force for 2-3 seconds (83). Participants were instructed to exhale during the

exertion of maximal force and received strong verbal encouragement. Visual feedback was displayed on a 50.5cm monitor as a vertically moving bar chart on a 0-100 scale (normalized to 100N). Custom LabView software was used to provide the visual feedback display (National Instruments cDAQ-1972 + NI-9215, 40Hz refresh rate). At least three MVC trials were performed with one minute rest intervals. MVC trials continued until two trials were within 5% of each other; this was generally achieved within 4 or 5 trials. The maximum force (N) was recorded. During the steadiness tasks similar visual feedback was provided, but was normalized to the subject's maximal force. Participants were instructed to increase to a target force set at 10% MVC and to maintain a steady contraction. Participants were given 1-2 practice trials followed by two trials at least 10 seconds in duration (83). Force output and surface EMG were recorded during these trials with data stored and analyzed off-line. The mean force, standard deviation of force, coefficient of variation of force (SD of force/mean force x100), and root mean square (RMS) of FDI and APB muscle activity were calculated and averaged for the 2 steadiness trials.

TMS Testing

Motor cortex stimulation was delivered with a 70 mm figure-of-eight shaped coil and two Magstim 200^2 stimulators connected through a bi-stimulation module (Magstim Ltd, UK). The coil was positioned with the handle pointing posterior along a sagittal axis. The stimulation area (hot spot) was determined as the point consistently producing the largest MEP amplitude in the FDI muscle. The FDI was used to determine the hot spot and motor threshold (MT) because it

presumably is similar to other intrinsic hand muscles and is involved in a lateral pinch task. Resting MT was determined as the lowest stimulus intensity that elicited an MEP of approximately 100 microvolts in at least three of six consecutive stimulations (84). Testing of intracortical inhibition (ICI) and intracortical facilitation (ICF) was similar to the paradigm provided by Chen et al. (85); the interstimulus interval was 2ms for ICI and 15ms for ICF. The conditioning stimulus (CS) was set at 90% of MT (subthreshold) and the test stimulus (TS) was set at 116% of MT (suprathreshold). Twelve stimuli for each condition (ICI, ICF, and TS-only) were delivered in random order and stored to analyze off-line. Peak-to-peak amplitudes were measured for each MEP and the mean and standard deviation were determined for each outcome. Values were excluded from the analysis if outside the bounds of ± 2 standard deviations; the mean was then recalculated for each condition (TS, 2ms, and 15ms). Responses obtained during ICI and ICF trials were normalized to TS-only trials (ratio of the ICI or ICF MEP to the TS-only MEP).

rTMS protocol

A Magstim Rapid magnetic stimulator (Magstim Ltd, UK) with an air-cooled 70 mm figure-of-eight shaped coil was used with the coil positioned in contact with the scalp overlying the hot spot determined during TMS testing. Motor threshold was reassessed with the rapid stimulator to determine the stimulation intensity for the rTMS. The stimulus intensity was set at 70 % of MT; if MT exceeded 100% maximal stimulator output, MT was recorded as “100”. All participants received 900 stimulations administered as 30 trains of 30 stimuli at

10 Hz (3s train duration and 30s inter-train interval; Figure 1). The functional-rTMS condition required subjects to generate summed muscle activity (FDI, APB, and FPB) that exceeded a threshold of 20% of the summed maximum EMG activity recorded during MVCs. A custom LabView application provided a visual cue to begin the pinch contraction (light turned on) and visual feedback was provided regarding the percentage of EMG produced. Subjects were instructed to maintain the contraction during the rTMS train and then asked to relax after the light turned off. Participants were given 2-3 practice trials prior to receiving stimulation. The control group received the same rTMS parameters and was instructed to remain at rest during the entire rTMS session. EMG activity of the FDI, APB, FPB, and biceps brachii were observed between stimulation trains to monitor post-rTMS muscle activation, as suggested by Chen et al.(86)

Immediately after completion of the rTMS, the lateral pinch steadiness trials and TMS measures were repeated. The target forces remained the same and were based on the initial MVC. Motor threshold was re-evaluated post-rTMS with the corresponding CS and TS intensities re-calculated.

Data Analysis

Descriptive statistics are presented as means ± standard deviations in the text and means ± standard error in figures. Bivariate correlations were computed to determine the relationships between the functional measures, MVC, MT, CV of force, RMS EMG, and TMS measures. Data were inspected for normality using the Shapiro Wilk's test and the TMS data transformed using the natural log to

achieve normality (ICI and ICF). An independent samples *t* test was used to verify group similarities at baseline for FM, MVC, and MT. Two-factor repeated measures analysis of variance (RMANOVA) with a between-subjects factor of stimulation condition and a within-subjects factor of time were used to compare mean force output, force steadiness (CV of force), muscle activity (RMS EMG), and TMS outcomes (ICI and ICF). Post hoc paired *t* tests were applied to determine pre-post changes within each group if there was a significant interaction effect. Change scores were calculated for CV, APB RMS, and TMS outcomes to determine the uniformity of rTMS responsiveness within groups and to quantify those relationships with correlation coefficients. The strength of the correlations were determined as follows: 0-0.25 little or no relationship; 0.25-0.5 fair relationship; 0.5-0.75 moderate to good relationship; and above 0.75 good to excellent relationship (63). Significance level was set at $p<0.05$.

Results

All participants completed the rTMS protocol without incident. Data from one subject was excluded from analysis because electrodes were dislodged and replaced during the protocol. As a result, nine participants completed the functional-rTMS protocol and eight received the passive stimulation. At baseline, there were no differences between groups for FM (t=1.1, p = 0.3), MVC force (t=1.1, p = 0.3), and MT (t= -0.9, p = 0.4). The MVC force was moderately strongly correlated with the FM test score (r = 0.5, p = <0.05) and the BBT score (r = 0.5, p <0.05). At baseline the MT was strongly correlated with the ICF values

for the FDI (r = 0.6, p <0.05) and APB (r = 0.5, p <0.05), but the ICI was not correlated with MT (FDI r <0.01 and APB r = -0.1).

Steadiness Tasks. The 10% target force was based on initial MVC value and was similar (F = 0.45, p = 0.8) before and after exposure to the rTMS protocol. Steadiness during the lateral pinch task, as expressed by the CV of force, changed differently for each stimulation group (time x condition interaction F = 6.3, p = 0.02). Directionally, the CV of force increased after stimulation for the functional-rTMS group and decreased for the passive stimulation group. The observed increase for the functional-rTMS group was not significant (t = -1.3, p = 0.1), but there was a significant decrease in the passive group (t = 2.1, p = 0.04).

Muscle activity. For the FDI muscle, the EMG activity during the 10% MVC contractions did not change after stimulation (F = 1.0, p = 0.3); the response was similar between groups (F < 0.01, p = 0.9). In contrast, there were differences between groups for the change in APB EMG activity (time by group interaction F=6.4, p = 0.02, Figure 3.3.). The increase in APB observed in the functional-rTMS group failed to reach statistical significance (t = -1.2, p = 0.1), and the decrease in APB activity for the passive stimulation group was significant (t = 3.5, p = 0.005). Six of the nine subjects in the functional-rTMS group had increased APB activity following the stimulation and six of the nine had a greater CV of force. In contrast, all but one of the subjects in the passive group exhibited a reduced CV of force after the rTMS and all had decreased APB activity.

TMS testing. The ICI for the FDI muscle did not change after stimulation ($F = 0.1$, $p = 0.8$) for either group ($F = 0.02$, $p = 0.9$, Figure 3.4). Similarly, ICF values for the FDI muscle were not different after stimulation ($F = 0.01$, $p = 0.9$) for either group ($F = 1.1$, $p = 0.3$). In contrast to the FDI, the ICI and ICF values for the APB revealed significant time by condition interactions ($F = 4.7$, $p < 0.05$ and $F = 6.1$, $p = 0.03$, respectively). Following functional-rTMS, the ICI for the APB muscle was significantly greater ($t = -2.2$, $p = 0.03$), whereas the passive group exhibited a non-significant decrease in ICI values for the APB muscle after rTMS ($t = 0.9$, $p = 0.2$). There was a significant increase ICF values in the APB muscle following the functional-rTMS ($t = -1.9$, $p = 0.048$). The passive stimulation group displayed a non-significant decrease in ICF values for the APB muscle following the rTMS ($t = -1.2$, $p = 0.13$). The values for change in APB EMG activity were moderately correlated with ICF change scores for the functional-rTMS group ($r = 0.6$, $p < 0.05$), but not for the passive-rTMS group ($r = 0.06$, $p > 0.05$).

Discussion

The findings of this study lend further support to the notion that magnetic brain stimulation can produce changes in cortical excitability sufficient to affect motor output. The main finding was that rTMS administered during voluntary muscle contractions ("functional-rTMS") produced different responses in motor performance and neurophysiological outcomes compared with rTMS delivered during rest. First, the functional-rTMS reduced inhibitory and increased facilitatory intracortical network responses observed in the APB muscle.

Secondly, the passive rTMS produced a decrease in APB activity and an accompanying decrease in the CV during the steadiness task. These results support our hypotheses and provide initial evidence for the potential to increase neuromotor descending output following functional-rTMS. We also observed a muscle-dependent modulatory effect after rTMS; significant changes for the APB muscle and no change for the FDI. This finding suggests that functional-rTMS may be used to differentially modulate muscle groups within the same cortical region, which may have clinical implications for survivors of stroke.

The ability to generate and maintain muscle activity during sustained contractions is often impaired following a stroke (80). During an isometric task that requires a constant maintained force level, the amplitude of fluctuations around the mean force can be used as an indicator of the ability to precisely modulate neuromotor activity (see Fig. 3.2). The CV of force is a normalized measure of the steadiness of an isometric force task (80, 87). The significant group by time interaction for the CV of force suggested that participants responded differently to each type of stimulation; the passive stimulation group improved steadiness after stimulation, as evidenced by a decrease in the CV of force. We also measured the amplitude of EMG activity during the pinch task to estimate changes in the gross neural command reaching the muscle. In parallel with the decreased CV of force, the passive stimulation group exhibited a reduction in APB EMG activity after stimulation. These findings suggested that following passive rTMS, participants were able to reduce the neuromotor drive and attendant signal-dependent noise (88) while maintaining the same force

level. The possibility exists that the reduction in command and noise resulted in a less variable force output by the muscle. In contrast, the group that received functional-rTMS exhibited a trend toward an increase in the amount of APB activity during the steadiness task and a trend toward an increased CV of force. Presumably the increased neural command was associated with a greater amount of variability in the command and a more variable output. These findings suggest that passive-rTMS produced a refinement in neuromotor drive while functional-rTMS produced the opposite effect. Although the changes following functional-rTMS were not statistically significant, the potential to increase neuromotor drive and muscle activity may be an important aspect of stroke recovery, since the primary deficits are related to a loss of descending excitatory input to spinal motorneurons. The potential to modulate neuromotor behavior with functional-rTMS suggests that future research should determine the effects of an intervention consisting of multiple sessions of functional-rTMS.

In parallel with the changes in APB EMG muscle activity during the force task, significant interactions were observed for ICI and ICF in the APB muscle. Such peripheral and central changes were not observed for the FDI muscle. These results align with previous reports of differential modulatory effects within the same cortical representations for hand muscles (23, 89). The mechanism presumably responsible for differences between hand muscles following functional-rTMS is altered synaptic efficiency within the horizontal intracortical networks. The cortical change may be dependent on the agonist muscle contributing to the motor task (90, 91). For example, Liepert and colleagues (89)

concluded that disinhibition enhanced the excitability of cortical neurons responsible for movement of agonist muscles. Our findings of less inhibition (ICI) and increased facilitation (ICF) following the functional-rTMS support these previous findings and strengthen the notion that the excitability of the cortical neurons for the APB muscle was enhanced. The ICI effect was likely mediated by down-regulation of GABA-ergic interneurons and the increase in the excitatory network (ICF) was related to glutaminergic excitation of corticocortical pyramidal cells (85). The summation of these inhibitory and excitatory effects presumably altered the overall input to corticospinal cells in the direction of excitability, as has been previously demonstrated (92).

We found changes in inhibitory and excitatory networks following functional-rTMS, but not following passive-rTMS. More specifically, the ICF change scores were significantly correlated with increases in APB EMG activity during a steadiness task following functional-rTMS but not passive-rTMS. We did not observe significant changes in ICI and ICF after passive stimulation – likely a result of the low stimulation intensity relative to motor threshold. For safety considerations, we chose a relatively low stimulation intensity to remain sub-threshold for both groups. The potential exists that this stimulus intensity failed to elicit the excitatory effects of high-frequency stimulation as previously described in passive-rTMS protocols (74, 76). The motor activity required of the functional-rTMS group during the rTMS likely lowered the motor threshold and increased the relative stimulation intensity. Future research should address the relation of

rTMS stimulus dose to cortical and neuromuscular response during passive- and functional-rTMS.

A secondary observation from our data suggested that the APB muscle was a primary contributor to the lateral pinch task in survivors of stroke, consistent with a previous report in neurologically intact subjects (93). Johanson et al. (93) demonstrated that the activity of the APB muscle was more regulated during lateral pinch compared with seven other intrinsic and extrinsic muscles of the hand including the FDI. The APB muscle is presumably preferentially regulated during a lateral pinch task when forces must be well-directed. These are important considerations because different neural circuits for muscles within the same cortical representation may be differentially activated when motor tasks are performed alone or combined with rTMS, (23, 89). For example, high-frequency rTMS applied during wrist flexion or extension preferentially impacted agonist muscles but not antagonists (23). We consistently demonstrated a similar effect for functional-rTMS in survivors of stroke considering that the APB is the primary agonist muscle regulated during a lateral pinch task. This may have important clinical stroke applications because functional-rTMS protocols could differentially modulate or target weaker muscle groups such as the wrist extensors. This should be explored in future studies.

Conclusion

These results provide initial support for the use of a functional-rTMS protocol to increase neural excitability in survivors of stroke following a single

rTMS session. In this study the congruence between our behavioral, neuromotor, and neurophysiologic outcomes produces a more complete and thus stronger understanding of the efficacy of the stimulation. We have extended the work of Fujiwara and Rothwell (23) by demonstrating the specificity of functional-rTMS on targeted brain circuits in survivors of stroke. The activation of target muscles that was required during functional-rTMS engaged selective neural circuitry, which appears to have been differentially impacted by the cortical stimulation. The full realization of the therapeutic potential of functional-rTMS will require additional studies that implement the protocol in a training intervention applied over longer periods.

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Table 3.1. Participant Demographics, divided by experimental condition

Subject	Age	Sex	Years Post-stroke	Stroke Hemisphere	Type of stroke	FM
Functional rTMS						
1	44	M	0.6	Right	Ischemic	48
2	71	M	4.2	Right	Ischemic	55
3	68	M	1.6	Left	Ischemic	60
4	54	M	0.8	Left	Ischemic	44
5	65	F	1.8	Left	Hemorrhagic	56
6	75	F	3.1	Right	Ischemic	57
7	51	M	3.5	Left	Ischemic	44
8	70	M	4.7	Left	Ischemic	61
9	64	F	3.7	Left	Ischemic	61
Mean ±SD	62 ±10		3±1.5			54±6.9
Counts		3F:6M		3R:6L	1 Hemorrhagic: 8 Ischemic	
Passive rTMS						
10	74	F	5	Right	Ischemic	50
11*	66	F	6.8	Left	Hemorrhagic	57
12	61	M	1.3	Right	Ischemic	60
13	74	M	4	Left	Ischemic	48
14	86	M	4.1	Right	Ischemic	47
15	63	M	13.8	Left	Ischemic	28
16	41	F	0.5	Right	Ischemic	60
17	63	F	3	Right	Ischemic	29
18	70	M	2.7	Right	Ischemic	63
Mean ±SD	66 ±12		5±3.9			49±13
Counts		4F:5M		6R:3L	1 Hemorrhagic: 8 Ischemic	

*Participant not included in analysis
Abbreviations: FM, Fugl-Meyer; R, right; L,Left;

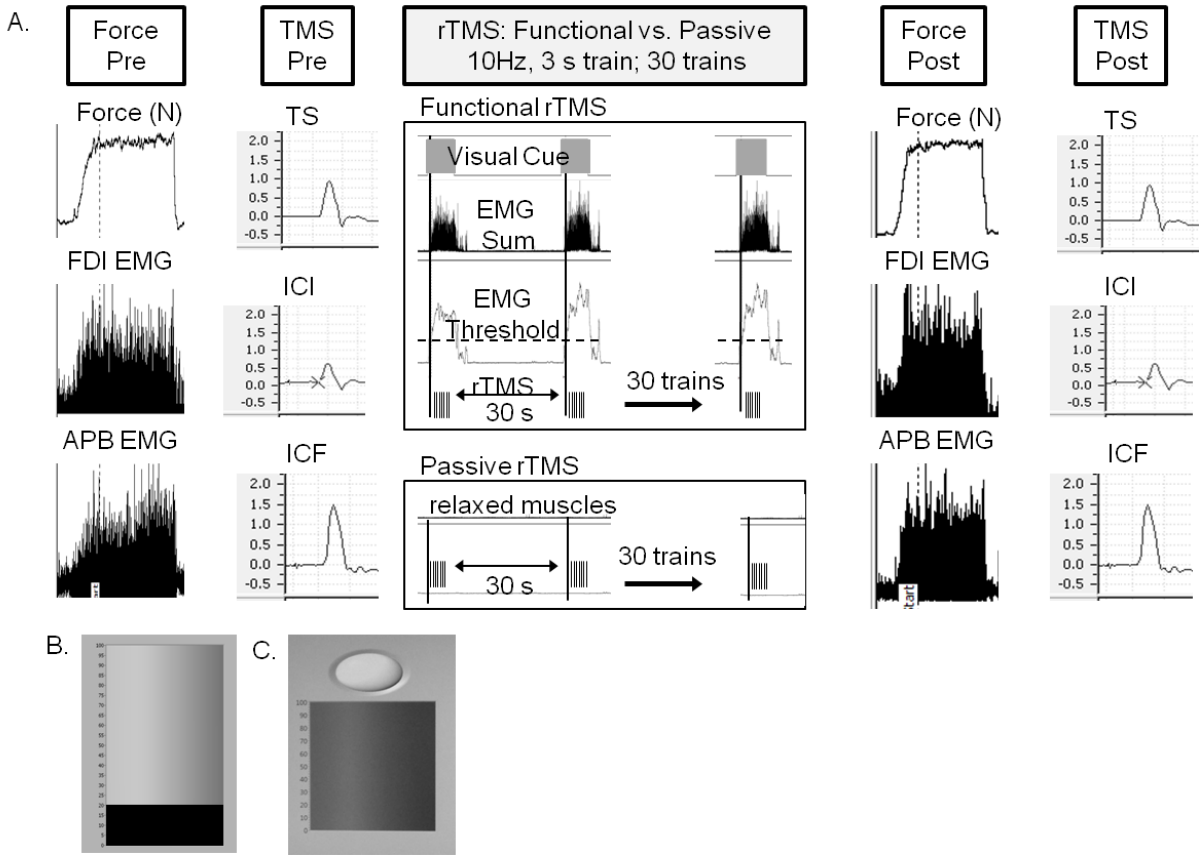

Figure 3.1. A. Schematic of experimental protocol. Force and TMS outcome measures were assessed before and after rTMS. B. Display of feedback during force steadiness trials. C. Display of EMG activity as feedback during functional-rTMS.

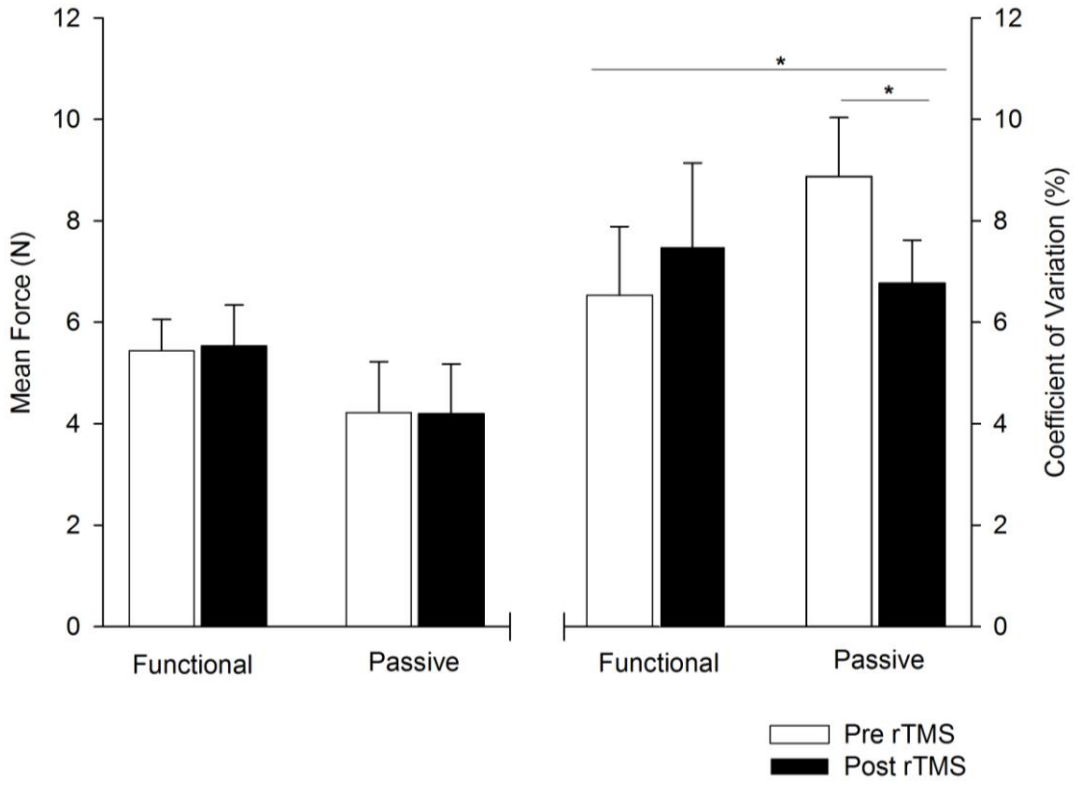

Figure 3.2. Mean force and coefficient of variation for 10% MVC steadiness task. There were no differences between the mean force levels between the two groups and the target force levels remained consistent post rTMS. There was a significant interaction in the CV of force, with a reduction in CV following passive-rTMS.

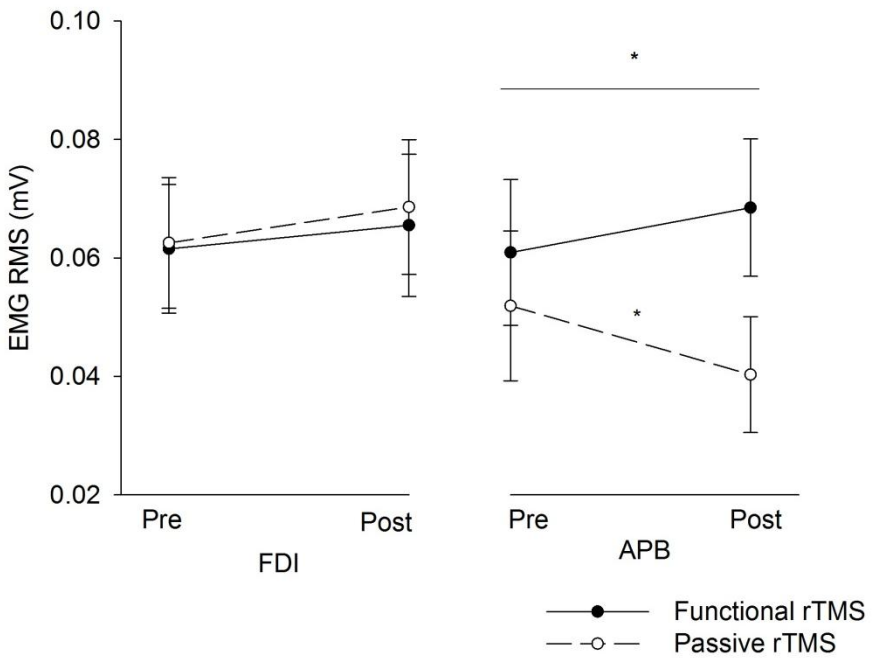

Figure 3.3. Muscle activation during 10% MVC steadiness task. The amount of FDI EMG activity did not change, but there was a significant interaction in the APB EMG activity. There was a significant reduction in EMG activity following passive-rTMS.

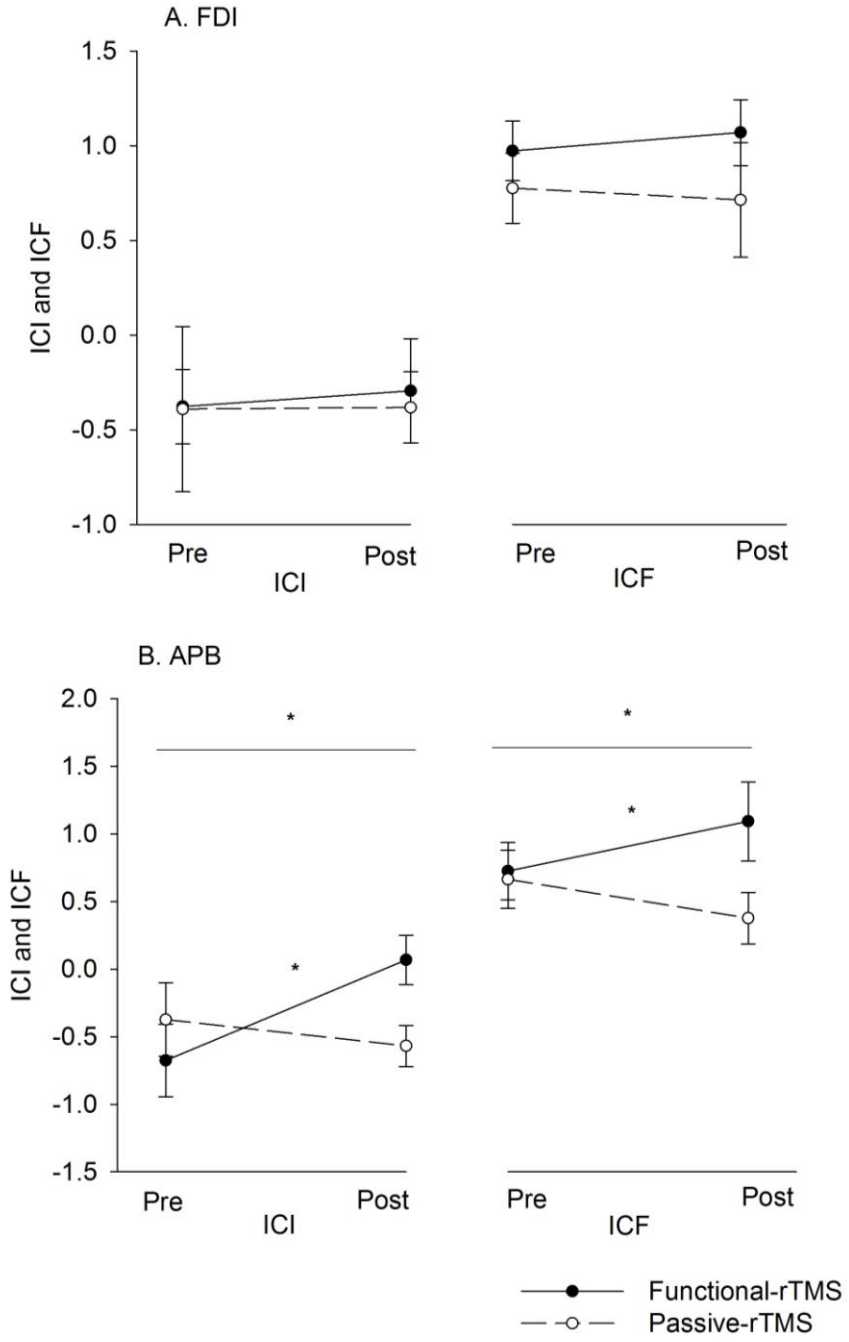

Figure 3.4. Intracortical inhibition (ICI) and intracortical facilitation (ICF) for FDI and APB. There were no differences in the FDI, but there were significant interactions for ICI and ICF in the APB muscle. There was significantly less inhibition and increased facilitation following functional-rTMS.

CHAPTER V – OVERALL CONCULUSIONS

Recovery from stroke is a complex and multi-faceted process with many factors influencing the degree to which motor impairments are remediated or resolved. Stroke rehabilitation efforts may involve intense and structured upper extremity interventions and/or applications such as rTMS to promote UDP. This collection of studies aids in the understanding of how the basic structure of the reaching task influences reaching strategies. These results can be used to further refine upper extremity interventions and assessments. Initial evidence also was provided that functional-rTMS can facilitate UDP to a greater degree than passive-rTMS, a finding that has important implications for future research studies in a stroke rehabilitation context.

We have previously demonstrated that differences in movement strategy changes following interventions may depend, in part, on the structure of the reaching task used within an intervention (8, 10). The detailed description of how discrete reaching is different than cyclic reaching extends many previous reports of kinematic motion analysis of upper extremity reaching in survivors of stroke that focused mainly on discrete tasks. Given that cyclic reaching is different than discrete, including cyclic tasks within interventions provides a unique opportunity to generate continuous motion while integrating real-time adjustments based on afferent feedback. Cyclic tasks should also be considered as an outcome measure because they capture a different motor control strategy and are

correlated with functional ability. Cyclic reaching in an intervention provides the opportunity to incorporate afferent feedback within the motor programming and incorporates repetitions of movement. A significantly smaller amount of anterior and posterior deltoid muscle activity in the stroke affected side suggests that motor control impairments may reside partially in the shoulder girdle. The relationship between muscle activation and kinematics, however, remains difficult to causally determine. Musculoskeletal modeling applications may be used to address this question by comparing muscle activation patterns generated from a model compared to experimentally derived values in both neurologically intact populations and in stroke. Additional use of technologies to better quantify scapular movement during reaching in stroke will also add to the knowledge of motor control impairments post-stroke. The stroke rehabilitation research community will continue to benefit from these advancements with the ultimate goal to improve outcomes for survivors of stroke.

The second aim was focused on better understanding the potential to increase the degree of UDP with functional-rTMS, a novel non-invasive brain stimulation protocol requiring subjects to voluntarily generate muscle activity to trigger each rTMS train. Repetitive TMS protocols promotes UDP by modulating cortical excitability presumably through changes in synaptic efficacy, yet direct evidence of this mechanism is not yet possible in humans (19). As a result, studying post-rTMS changes in humans are limited to the level of neural networks or global measures of excitability (19). Paired-pulse techniques can reveal changes in the inhibitory and facilitatory networks, yet the balance of these

systems is critical for motor control studies. Our study demonstrated the potential to generally increase the excitability of the primary motor cortex of the stroke-damaged hemisphere following functional-rTMS because we observed less inhibition *and* more facilitation. A potential mechanism for this effect following functional-rTMS is that the engagement of the motor cortex during the lateral pinch task primed the facilitation response and down-regulated the inhibitory networks. A similar outcome has been observed with voluntary muscle activation during paired-pulse testing for ICI (91). These findings may represent enhanced facilitatory circuits, suppressed inhibitory circuits, or a combination of both, but a definitive conclusion is not yet possible (19). Although these should still be considered presumed or potential mechanisms for functional-rTMS, the consistency in the general degree of change for ICI and ICF pre to post is important to note, and suggests that both networks (facilitatory and inhibitory) may contribute equally. Additional research, and/or new technologies, will be required to further provide this important evidence. A secondary observation was that the neural networks of the agonist muscle involved in a lateral pinch task were modulated following functional-rTMS, but not in the antagonist muscle. This is an important consideration for stroke rehabilitation because facilitating specific muscle groups (e.g., wrist extensors) may be accomplished by engaging those muscles during functional-rTMS. Additional research should also address the potential applications of functional-rTMS as intervention by using additional sessions to determine lasting effects of the protocol on motor control outcomes.

This collection of studies is a direct response to reviews calling for more mechanistic research for stroke rehabilitation. Given that previous research has demonstrated the efficacy of structured, intense interventions to facilitate use-dependent plasticity following a stroke, the systematic approach used in the current studies contribute to uncovering the elements of interventions that may be responsible for the global improvements observed following an intervention. The current studies directly contribute to a more solid evidence base for complex interventions that incorporate technological approaches such as rTMS combining with structured reaching protocols.

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APPENDIX A – HUMAN SUBJECTS APPROVAL

Colorado State University

Knowledge to Go Places

Research Integrity & Compliance Review Office
Office of the Vice President for Research
321 General Services Building - Campus Delivery 2011
Fort Collins, CO
TEL: (970) 491-1553
FAX: (970) 491-2293

NOTICE OF APPROVAL FOR HUMAN RESEARCH

DATE:	August 17, 2010
TO:	Malcolm, Matthew, 1573 Occupational Therapy
	Browning, Ray, 1582 Dept Hlth & Exer Sci, Massie, Crystal, 1573 Occupational Therapy, Wood, Wendy, 1573 Occupational Therapy
FROM:	Barker, Janell, CSU IRB 1
PROTOCOL TITLE:	EMG-Triggered Functional Motor Cortex Stimulation in Stroke.
FUNDING SOURCE:	American Heart Association : 100040
PROTOCOL NUMBER:	10-1784H
APPROVAL PERIOD:	Approval Date: August 12, 2010 Expiration Date: July 15, 2011

The CSU Institutional Review Board (IRB) for the protection of human subjects has reviewed the protocol entitled: EMG-Triggered Functional Motor Cortex Stimulation in Stroke.. The project has been approved for the procedures and subjects described in the protocol. This protocol must be reviewed for renewal on a yearly basis for as long as the research remains active. Should the protocol not be renewed before expiration, all activities must cease until the protocol has been re-reviewed.

If approval did not accompany a proposal when it was submitted to a sponsor, it is the PI's responsibility to provide the sponsor with the approval notice.

This approval is issued under Colorado State University's Federal Wide Assurance 00000647 with the Office for Human Research Protections (OHRP). If you have any questions regarding your obligations under CSU's Assurance, please do not hesitate to contact us.

Please direct any questions about the IRB's actions on this project to:

Janell Barker, Senior IRB Coordinator - (970) 491-1655 Janell.Barker@Research.Colostate.edu
Evelyn Swiss, IRB Coordinator - (970) 491-1381 Evelyn.Swiss@Research.Colostate.edu

Janell Barker

Barker, Janell

Includes:

Approval is for a maximum of 30 participants over the age of 18. Consent will be obtained with the approved consent form that is in eProtocol. One condition of approval is that any DSMC reports obtained will be submitted to the IRB for review and to be placed in the file.

Approval Period:	August 12, 2010 through July 15, 2011
Review Type:	FULLBOARD
IRB Number:	00000202
Funding:	American Heart Association : 100040

APPENDIX B – INFORMED CONSENT

Consent to Participate in a Research Study
Colorado State University

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

PRINCIPAL INVESTIGATOR: Matt Malcolm, Ph.D., OTR
Department of Occupational Therapy
Colorado State University
Fort Collins, CO 80524
(970) 491-2646
malcolm2@cahs.colostate.edu

CO-PRINCIPAL INVESTIGATOR: Crystal Massie, MS, OTR
Department of Occupational Therapy
Colorado State University
(970) 491-3444

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

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

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

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

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

Once the researchers have verified that you meet all study criteria, you will be asked to participate with the initial evaluation. This and all other evaluation sessions will allow the researchers to determine how well you are able to use your stroke-affected arm and hand, and to evaluate the activity level of your nervous system. Testing will occur over two separate sessions (a morning and an afternoon testing

session) each lasting approximately 2 to 3 hours. The following section describes the tests that will be done in the morning and afternoon initial testing sessions and what we will ask you to do during these tests. Once accepted into the study, you will need to come to the Colorado State University campus for a total of six days. The total number of hours involved in full participation in the study is approximately 20 hours.

Initial Evaluation Session (Pre-test)

MORNING SESSION
Location: Physical Activity Laboratory, Health and Exercise Science

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

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

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

<BREAK/LUNCH>

AFTERNOON SESSION
Location: NeuroRehabilitation Research Laboratory, Occupational Therapy

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

Transcranial Magnetic Stimulation testing: Using the same muscles and electrodes from the previous test, we will next assess the part of your nervous system that controls those muscles using transcranial magnetic stimulation (TMS). During the stimulation you will be seated in a comfortable chair. We will place a cloth cap on your head so that we are able to keep track of where we stimulate with the TMS. The magnetic stimulation uses changes in magnetic fields in the brain producing electrical currents, which may affect brain activity and function. You will experience two different types of TMS in this testing. First, we will use single and paired pulses of TMS to measure the activity of your nervous system. Then we will use repetitive pulses of TMS, which will be a short and fast burst of TMS lasting 3 seconds. This will be followed by 30 seconds of rest, and then another short burst of fast TMS. This procedure will last approximately 20 minutes. We will then again use single and paired pulses to measure the activity of your nervous system.

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

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

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

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY?
You may be excluded from participating if any of the following are true:

- You have had or could have a seizure
- You have a history of epilepsy
- You have a pacemaker or other implanted device or metal object in your head or neck
- You take medications that could increase your risk for having a seizure
- You have had a brain injury leading to loss of consciousness within the last year
- You have had or currently have a brain tumor
- You have mental retardation, uncontrolled psychiatric or medical illness, or uncontrolled heart disease
- You are pregnant
- You are younger than 18 years of age

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

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

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

Transcranial Magnetic Stimulation (TMS):
TMS is considered a non-invasive technique to activate brain cells. There are, however, some risks associated with TMS. One primary risk factor is the possibility of a seizure occurring. Guidelines to prevent seizures caused by TMS have been published and will be followed in conducting this study. TMS may cause a seizure in individuals that have a history of epilepsy or previous seizures. For this reason, any individual who has a history of epilepsy or seizures will be excluded from this study. TMS may also

interfere with devices such as a heart pacemaker or deep brain stimulator. For this reason, individuals who have a pacemaker or other metal implants in the head, neck or upper body, will be excluded from this study. The Investigator will ask you if you have a history of seizures or epilepsy, and if you have a pacemaker or other implanted metal device. Certain medications can increase the risk of a seizure occurring during TMS. For this reason, one section of the health questionnaire asks you to list medications you currently take and the dosage for each. This list will be reviewed by the study physician. If you are taking a medication that could increase the risk of having a seizure and you are unable to safely stop taking the medication, you will not be allowed to participate. **Importantly, if you stop taking any of these medications or you start taking a new medication or different dose of medication during your time in the study, you must immediately notify the researchers.** The study physician will review any such changes in your medications and you may have to stop participating in the study if the changes could increase your risk for having a seizure.

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

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

1. Muscle responses will be monitored with electromyography (EMG) equipment during and after stimulation. EMG will allow the investigators to measure and monitor muscle responses during and after TMS. If the TMS causes a spread of excitability or lasting excitation in your muscles, the investigators will see this on the EMG. If this occurs, TMS will be stopped.
2. If a seizure does occur, medical attention will be immediately requested by the investigators.

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

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

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

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

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?
The benefits to you include improved knowledge about your abilities and possibly improving your movement abilities. Also, the information that comes out of this study may help improve the treatment of stroke in the future.

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

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

WHO WILL SEE THE INFORMATION THAT I GIVE?
We will keep private all research records that identify you, to the extent allowed by law.
Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep you name and other identifying information private.

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

CAN MY TAKING PART IN THE STUDY END EARLY?
You may be withdrawn from the study *without* your consent for the following reasons:

- You need a treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- Study procedures have a bad effect on you.
- You are not able to keep appointments.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?
You will be compensated a total of $75 for participating in the study; which will be separated into two payments. The total payment will be broken down as follows:

- $50 paid following completion of the post-test.
- $25 paid following completion of the 1-month follow up test.

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

WHAT IF I HAVE QUESTIONS?
Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Matt Malcolm, PHD at (970) 491-2646. If you have any questions about your rights as a volunteer in this research, contact Janell Barker, IRB Senior Administrator at 970-491-1655. We will give you a copy of this consent form to take with you.

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

_____ _____
Signature of person agreeing to take part in the study Date

_____
Printed name of person agreeing to take part in the study

_____ _____
Name of person providing information to participant Date

_____
Signature of Research Staff