THE CATHOLIC UNIVERSITY OF AMERICA

Robotic Retraining of Hand Function Following Neurological Injury

A DISSERTATION

Submitted to the Faculty of the

Department of Biomedical Engineering

School of Engineering

Of The Catholic University of America

In Partial Fulfillment of the Requirements

For the Degree

Doctor of Philosophy

By

Sasha Blue Godfrey

Washington, D.C.

2012

Robotic Retraining of Hand Function Following Neurological Injury

Sasha Blue Godfrey, PhD

Director: Peter S. Lum, PhD

Most stroke survivors have some upper extremity impairment. Because the hand is crucial to many activities of daily living, limited hand function can have wide-ranging effects on one's independence post-stroke. Robotic rehabilitation is emerging as a tool to increase access to and dosage of therapeutic exercises while minimizing the cost and labor burden of rehabilitative therapy. The Hand Exoskeleton Rehabilitation Robot (HEXORR) is a novel system designed to retrain hand function following stroke. This thesis examines the neurophysiological effects of HEXORR practice, compares HEXORR's Tone compensation to another assistance method, and examines the benefits of HEXORR training post-stroke.

To examine the neurophysiological effects of HEXORR training, we created a bias such that one muscle is used over its antagonist throughout a training session. We then trained healthy volunteers on the device and measured physiological changes using transcranial magnetic stimulation. We found response to training varied based on the muscle used in the task rather than the muscle's role as an agonist or antagonist in the task. This information can be used to improve treatment plans for stroke patients.

Oftentimes, robotic assistance is modeled after a spring attaching one's limb to a target. The further one is from the target, the larger the force produced by the robot to assist in reaching the target. In contrast, HEXORR uses Tone Assistance, a method based on the user's own hypertonicity, resulting in increased assistance as one nears the target. We compared the performance of stroke patients using these two modes and found that the Tone mode encourages the user to be more engaged in the training and enables more natural torque patterns to produce these movements.

Finally, we conducted a training study with 8 stroke patients in which they trained with HEXORR for 18 sessions. We measured their progress by comparing clinical measures of impairment before and after training and at follow-up. Overall, we found subjects stratified into lower and higher impairment groups which were related to outcome. Those with higher impairment improved only in range of motion and grip strength whereas those with lower impairment improved on a range of clinical scales.

This dissertation by Sasha Blue Godfrey fulfills the dissertation requirement for the doctoral degree in Biomedical Engineering approved by Peter S. Lum, PhD, as Director, and by Sang Wook Lee, PhD, and Michelle Harris-Love, PT, PhD, as Readers.

Peter S. Lum, PhD, Director

Sang Wook Lee, PhD, Reader

Michelle Harris-Love, PT, PhD, Reader

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

ACKOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Peter Lum for welcoming me into his lab and providing me with the guidance and support needed to succeed in a graduate program.

I also thank Dr. Michelle Harris-Love for her collaboration and mentorship.

There were many "behind the scenes" people who helped collect and interpret data and work through research questions. I would like to acknowledge Rahsaan Holley, Dr. Chris Schabowsky, Tony Metzger, Beth Brokaw, and Evan Chan for their assistance over the course of my graduate career.

Finally, I am extremely grateful for the love, support, and especially patience of my family, without whom this work would not have been possible.

I. BACKGROUND

A. *Neurological Injury*

In the United States alone, nearly 800,000 people experience a stroke each year; over 600,000 of which are first attacks (Lloyd-Jones et al 2010). Worldwide, there are 15 million strokes per year, of which 5 million result in permanent disability (World Health Report 2002). A stroke, also known as a cerebrovascular accident, is a condition wherein blood flow to part of the brain has stopped. There are two distinct types: ischemic, caused by a blocked vessel, and hemorrhagic, caused by a vessel rupture. Regardless of the type of stroke, lack of blood flow deprives the brain of oxygen, resulting in cell death.

The outcome of a stroke depends largely on the size and location of the brain that was deprived of blood and oxygen. Though between 50 and 70% of stroke survivors regain functional independence (Lloyd-Jones et al 2010), nearly 80% of survivors have upper extremity hemiparesis (Heart Disease and Stroke Statistics 2005). Limited hand function and range of motion often stem from spasticity (stretch reflex), hypertonia (excessive resistance to movement), or muscle weakness (Kamper et al 2003). In large part because of a combination of spasticity and/or hypertonia of the finger flexors and weakness in the finger extensors, the most salient pattern of post-stroke hand impairment is to have greater difficulty activating the finger extensors than the finger flexors.

B. *Rehabilitation*

Studies have found increased dosage has a positive effect on rehabilitation therapy (Riener et al 2005, Dromerick et al 2006) and repetitive, task-specific movements are effective at rehabilitating the upper extremity after stroke (Prange et al 2006). The advent of rehabilitation robotics has enabled increased use of both of these methods while achieving results comparable to conventional therapy and reducing the cost and labor burden (Lum et al. 2002, Timmermans et al. 2009). Robot-aided therapy allows a wide array of practice conditions including assisted or resisted exercises or passive motion (Kwakkel et al. 2008, Lum et al. accepted) and may provide a simple, objective mean to measure patient progress (Bosecker et al 2010). Despite the myriad potential benefits of robotic therapy, more research is needed to determine the most effective means of treating upper extremity impairments.

Hand function is essential for many activities of daily living; however, rehabilitation robots targeting the upper extremity originally focused on the proximal arm (Prange et al 2006, Kwakkel et al 2008, Kahn et al 2006). Increasingly, robots for the distal arm are being developed and evaluated (Balasubramanian et al 2010). Because optimal training methods have yet to be identified, many different therapeutic strategies are currently being evaluated. For example, the HandCARE and CyberGrasp both allow individual finger movement (Dovat et al 2008, Adamovich et al 2009). In contrast, the PneuGlove and Haptic Knob train opening and closing of the hand as a whole (Fischer et al 2007,

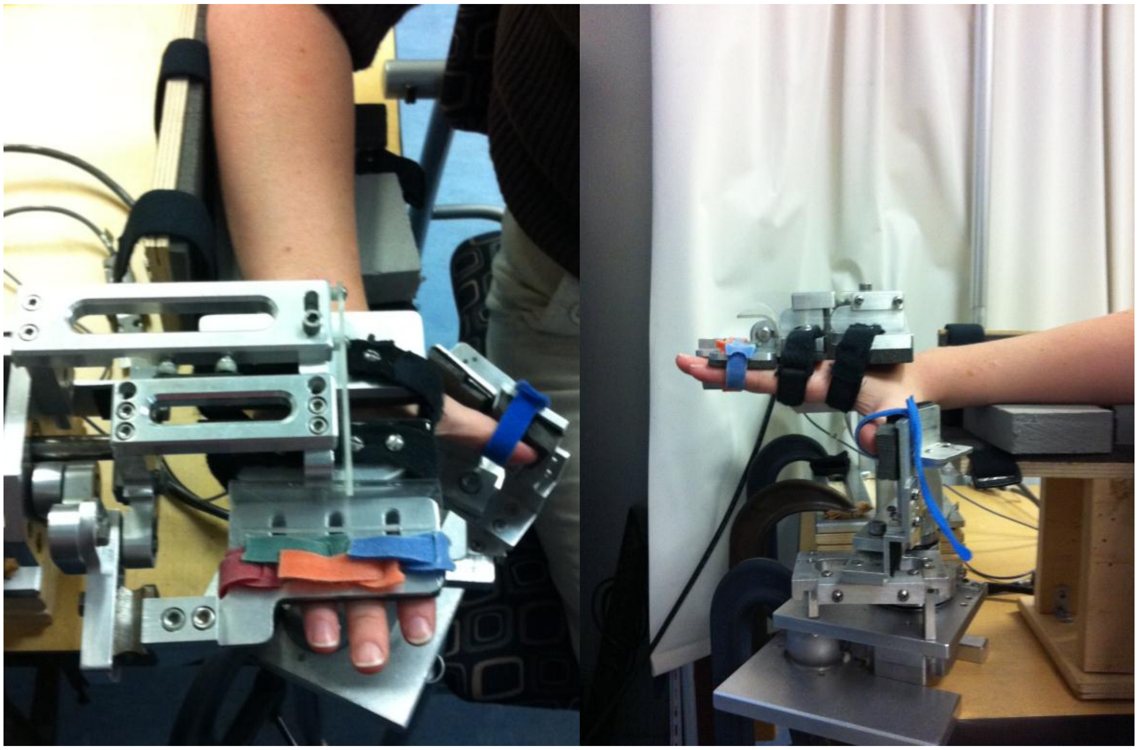

Fig. I.1: HEXORR-user interface top view (left) and side view (right) with hand in fully extended position.

Lambercy et al 2007). Still others combine wrist and finger training, such as the Hand Mentor and HWARD (Koeneman et al 2004, Takahashi et al 2008). While further work is needed to establish optimal training methods, as a whole, the application of robotics to hand rehabilitation has yielded positive results (Balasubramanian et al 2010).

C. *HEXORR*

The Hand Exoskeleton Rehabilitation Robot (HEXORR, Fig. I.1) was developed by the Center for Applied Biomechanics and Rehabilitation Research to retrain hand control and function. A complete description of the robot can be found in (Schabowsky et al 2010). In brief, the hand and arm are stabilized by a palmar strap and a forearm support. The robot linkages control the finger metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and the distal interphalangeal (DIP) joints are left free. The four fingers function cooperatively as one unit and the movements of the MCP and PIP joints are synchronized. The robot can be adjusted for variations in hand size and finger length. The distal end of the thumb is attached to a crank-and-slider mechanism that ensures coordinated motion of the three thumb joints: interphalangeal (IP), MCP, and carpometacarpal (CMC). For subjects who required more stabilization, the robot was also attached to the thumb at the IP and MCP. The thumb component can move vertically to achieve optimal fit for each subject. It also can rotate on a gimble to allow a C-grasp or key-pinch grasp pattern. From the fully flexed position, the fingers can extend up to 80º at the MCP and PIP joints (approximately 10º from full extension) and 90º at the interphalangeal joint of the thumb.

The finger and thumb components function independently and are driven by separate motors. The motors provide gravity, static friction, and dynamic friction compensation. Both components employ a digital encoder (resolution 0.0005° and 0.0002°, respectively) and torque sensor (TRT-200, Transducer Techniques, Temecula, CA) with a max of 22.6 Nm of flexion/extension torque. These are used both online for feedback during the therapy modes and offline as a user assessment tool. HEXORR has multiple exercise modes: it allows the user to move with or without assistance, can block motion to enable isometric exercises, and can provide passive motion. A passive stretch mode allows users to acclimate to the robotic environment and provides an assessment tool for investigators to quantify tone. A range of motion (ROM) mode gives the user an opportunity to reach his/her maximal ROM before finishing the movement. To practice and develop range of motion, a Gate Game mode was developed, described in Chapter III. To respond to the challenge of finger spasticity and hypertonia and extensor weakness, we developed a novel tone compensation algorithm for use with the Gate Game. This algorithm will be described in detail later; in brief, the motor torque required to passively move the fingers and thumb through its range of motion is provided during active motion to counterbalance the user's hypertonia. The last HEXORR mode is an isometric Squeeze Game in which users are held in a static position and required to practice grasp and release. To increase user motivation and enjoyment, HEXORR users interact with a simple computer game while exercising with the device.

D. *Thesis Aims*

Examine neurophysiological changes induced by HEXORR training

The first aim of this thesis was to examine the neurophysiological changes induced by HEXORR training to ultimately inform the development of future stroke rehabilitation protocols. A variety of robotic methods are currently in use including passive, assisted, and bimanual exercises; however, the most effective methods of retraining hand function have not been fully elucidated. Studies have shown that the benefits of repetitive task practice in stroke populations are partly due to cortical plasticity (Dimyan & Cohen 2011, Nudo 1999), thus one method to evaluate different robotic therapy methods is to study their effects on the motor cortex. Transcranial magnetic stimulation (TMS) is a method of examining cortical physiology and can be used to measure muscle representations, corticospinal excitability, and intracortical or interhemispheric inhibition. Repetitive motor practice can induce such changes as increased corticospinal excitability and decreased short-interval intracortical inhibition in the agonist muscle for the practiced task (prime mover) that are not apparent in the antagonist muscle (Pascual-Leone et al. 1995; Liepert et al. 1998; Classen et al. 1998, among others). It is not known, however, if this phenomenon is a result of the muscle itself or the agonist role it plays in the task.

As described above, stroke survivors face distinct challenges when it comes to finger flexor and extensor control. Understanding the differences between finger flexors and extensors in response to motor practice may lead to more effective training protocols. To that end, we examined the neurophysiological effects of a single bout of repetitive, goal-directed practice on finger flexor vs. extensor muscles in healthy volunteers, and tested for possible differences based on whether each muscle acted as the agonist or antagonist during the practiced movement. In both healthy individuals and stroke survivors, practice-dependent motor cortex plasticity can be observed after a single session of repetitive use or practice (Classen et al. 1998; Jensen et al. 2005; Liepert et al. 2000).

We used TMS to examine the physiological effects induced by robotic hand training with HEXORR. HEXORR was programmed to apply resistive forces to the hand during repetitive movement practice tracking a pseudo-random, sinusoidal waveform. The resistance created a bias against one muscle (the finger flexors in one training session and the extensors in another) that resulted in that muscle acting as the prime mover for both flexion and extension movements. This experimental setup enabled testing of each muscle as an agonist and antagonist to determine if there is a difference in the neural effects of training when acting as an agonist or antagonist.

Compare HEXORR's novel tone compensation to an alternative oft-used method

The second aim of this thesis was to compare the novel tone compensation used with the HEXORR device to another assistance method often used in robotic rehabilitation. Evidence is emerging that user engagement plays an important role in therapeutic outcome (Guadagnoli & Lee 2004). One common approach used to provide robotic assistance resembles a linear spring: as distance to the target increases, so does the magnitude of the assistance provided (Roy et al 2009, Nef et al 2006, Krebs et al 2003, Marchal-Crespo 2010). This method, dubbed "Spring mode", emulates the effect of connecting one's limb to the target with a physical spring with zero rest length; the spring stiffness can be adjusted to modulate the assistance provided.

While there is logic to providing maximal assistance at the point furthest from the target, hypertonia, which limits finger extension post-stroke, exhibits a roughly linear profile that increases with extension. In contrast to the Spring mode, HEXORR compensates for the user's tone profile directly by measuring the hand's passive resistance to stretching and providing assistance during movement to counterbalance the measured tone. This "Tone mode" results in assistance that increases with extension. In this study, subjects played a range of motion based game (described in detail in Chapter III) with each mode. To encourage active participation, Spring mode is occasionally used with a delay: one is given the opportunity to engage the task unassisted and assistance is provided after a delay to finish the task. For completeness, we tested four conditions: with Tone or

Spring mode on during the duration of the movement phase or with Tone or Spring mode on in the second half of the movement phase (determined by time, not distance). To optimize the amount of assistance provided, each mode was used in conjunction with an auto-adaptation algorithm that altered the assistance provided to better match the subject's ability level. We then compared these to an unassisted baseline in terms of user work, robot work, displacement, and success rate to evaluate each mode.

Examine the benefits of HEXORR training and determine target population

The third and final aim of this thesis was to examine the benefits of and determine the optimal population for HEXORR training. We conducted a training study in which seven chronic stroke subjects each received 18 sessions of 1-1.5 hours of HEXORR training. To evaluate the therapeutic benefits of the training, clinical and range of motion measures were taken for each subject before starting the training, after completing the 18 sessions. These measures were again taken at a three-month followup to determine retention. The clinical measures consisted of standard tests of impairment including the upper extremity Fugl-Meyer, to measure overall impairment, and the Action Research Arm Test, to measure hand impairement. Range of motion data was gathered using the CyberGlove (CyberGlove Systems LLC, San Jose), a glove with built-in bend sensors that allow real-time kinematic recordings.

Each training session consisted of two evaluation and two training modes (details provided in Chapter IV). A stretch routine was used to measure tone on a daily basis and to provide the starting point for the Tone assistance mode. Range of motion in HEXORR was also tested daily. The bulk of the training consisted of playing a game practicing moving through one's range of motion with assistance provided by the novel tone compensation mentioned earlier. Roughly 25% of the training was spent playing an isometric game designed to focus on grasp and release. We examined changes in clinical measures and range of motion to determine the benefits of HEXORR training and identify the most responsive population.

II. THESIS AIM I: EXAMINE THE PHYSIOLOGICAL EFFECTS OF HEXORR HAND TRAINING

Portions of the following chapter were submitted for publication to the Journal of Neurophysiology under the title "Cortical effects of finger flexion- vs. extension-resisted robotic motor practice: A TMS study."

A. *Chapter Summary:*

Post-stroke arm rehabilitation can be facilitated by robotic devices; however, optimal training parameters are unknown. To better understand the physiological effects of motor practice in healthy individuals, previous studies have examined the cortical effects of practice primarily on the task agonist (prime mover), though some have examined effects on the antagonist as well. Importantly, the effects may differ when the same muscle acts as agonist or antagonist in the practiced task. To that end, practice-related cortical plasticity was examined in healthy volunteers performing a robotic waveform tracking task with the extensor digitorum communis (EDC) or flexor digitorum superficialis (FDS) acting as either the agonist or antagonist. Transcranial magnetic stimulation (TMS) was used to measure corticospinal excitability (CE) and short-interval intracortical inhibition of lower- and higher-threshold corticospinal neurons ($SICI_L$ and $SICI_H$, respectively) before and after a flexion- or extension-resisted finger tracking task. After

practice, the EDC had a significant decrease in $SICI_L$ with no change in CE, while the FDS had a significant increase in CE with no change in $SICI_L$, regardless of either muscle's action as agonist or antagonist. Irrespective of muscle, $SICI_H$ tended to increase or decrease with practice as an agonist or antagonist, respectively. We conclude that there is a difference in practice-related plasticity for finger flexor vs. extensor muscles, and perhaps differential modulation based on agonist vs. antagonist muscle roles in the practiced task. Thus, robotic rehabilitation paradigms should consider the muscles involved, their functional role in the practiced tasks, and the desired physiological effects.

B. *Introduction*

We used the Hand Exoskeleton Rehabilitation Robot (HEXORR) to apply resistive torques to the fingers during grasp-like movements (Godfrey et al. 2010; Schabowsky et al. 2010). The practiced task was a skilled, goal-directed, visually-guided, finger tracking task which required graded finger flexion and extension movments. We compared the corticospinal excitability and intracortical inhibition of the extensor digitorum communis (EDC) and flexor digitorum superficialis (FDS) in healthy controls before and after a single session of finger tracking practice with sustained resistance applied either to the finger flexors or extensors during practice. The primary objective of the study was to determine, within each muscle, whether there is a difference in the neural effects when that muscle acts as an agonist vs. antagonist for the practiced task. At the same time, we addressed the question of whether there is a difference in the neural effects of practice on flexor vs. extensor muscles of the hand.

C. *Materials & Methods*

Participants:

Ten right handed, healthy subjects participated in this study (ages 19-35, mean 25.7±4.8 yrs**;** 6 females). Participants had no history of neurological, neuromuscular or musculoskeletal disorders and had no contraindications to magnetic resonance imaging or TMS. All participants provided written informed consent according to a protocol approved by the MedStar Health Research Institute Institutional Review Board.

Study Design:

Participants underwent two practice sessions separated by at least a one-week washout period. During practice, resistance was provided to either finger flexion or finger extension, order counterbalanced. Each session consisted of roughly a one-hour TMS evaluation before and after a 45-minute robot practice session.

Testing Procedures:

Surface electromyography (EMG) electrodes were placed on the EDC and FDS muscles of the right arm. Muscles were located and electrode position confirmed according to the methods described by (Perotto et al. 2005). The amplified EMG signals were filtered (bandpass, 10 Hz to 3 kHz), sampled at 10 kHz, and stored on a personal computer for off-line analysis. TMS testing was performed using a MagStim200 stimulator (Jali Medical Inc., Woburn, MA) and a figure-of-eight coil with outside wing diameters of 9.5 cm. The coil was held tangentially to the scalp with the intersection of the two wings at a 45 deg angle to the midline, in order to induce electrical current in the cortex in the posterior–anterior direction (Brasil-Neto et al. 1992; Kaneko et al. 1996). The optimal coil location relative to the scalp (i.e. hotspot) was chosen as the location that consistently produced the largest peak-to-peak amplitude of motor evoked potentials (MEPs) recorded in both the EDC and FDS. Real-time neuro-navigation, using each participant's own high-resolution MRI scan (Brainsight™, Rogue Research, Montreal, Quebec), was used to record the coil position corresponding to the motor "hotspot" and ensure that the same location was used before and after practice and for both sessions.

Resting motor threshold (RMT) was determined by identifying the lowest stimulation intensity that produced at least five positive responses out of ten in the EDC. A positive response was defined as at least 50 µV MEP peak-to-peak amplitude. An input/output, or recruitment curve (RC), was collected by recording the responses to ten pulses at 90-

150% RMT intensity, in increments of 20%. The effect of short-interval intracortical inhibition on both lower- and higher-threshold corticospinal output neurons was measured as well ($SICI_L$ and $SICI_H$, respectively). The procedures for this measurement have been described in detail previously (Kujirai et al. 1993). Briefly, test stimuli (TS) were delivered either alone (single-pulse stimulation) or preceded 3 ms by a sub-threshold conditioning stimulus (CS; paired-pulse stimulation). The CS intensity was kept constant at 80% of RMT and the intensities of the TS were either 120 or 150% RMT (representing activation of lower- and higher-threshold corticospinal outputs, respectively). SICI of lower- and higher-threshold output neurons was tested separately, with 15 paired and 15 single pulses presented in random order. Importantly, the CS intensity needed to produce SICI has been shown to be unrelated to the strength or excitability of the corticospinal output neurons that are being inhibited (Chen et al. 1998). Therefore, the conditioning stimulus (CS) was kept constant to keep the amount of inhibition elicited relatively constant as well. Instead of varying the CS, the TS intensity was varied in order to recruit lower vs. higher-threshold corticospinal output neurons. Since there has been shown to be a small difference in the amount of SICI recorded when the TS intensity is varied (Chen et al. 1998; Daskalakis et al. 2002; Garry & Thomson 2009), we did not directly compare SICI of low vs. high threshold output neurons. Instead, these measurements were treated as separate dependent variables and compared before vs. after tracking practice.

Tracking Practice Procedures:

The finger tracking task was completed using the HEXORR, Fig II.1A. For this study, the thumb component was driven by, and synchronized with, finger motion. Digital encoder and torque sensor measurements were sampled at 200 Hz for off-line analysis. EMG data recorded during tracking practice was amplified, sampled at 1 kHz and stored for off-line analysis.

Each practice session included isometric maximum voluntary contractions (MVC) performed before and after tracking practice. The measurement before practice was used to set the amount of resistive torque applied during the practice session. The post-training

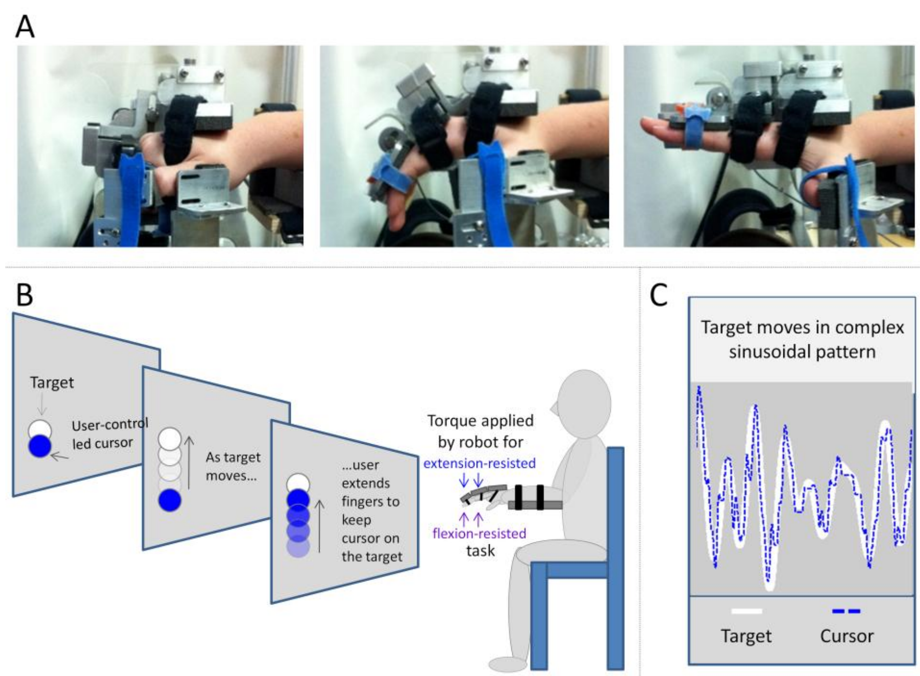

Fig. II.1: A) HEXORR-user interface at fully flexed, midway, and fully extended positions. B) Schematic of tracking task and setup. C) Sample of waveform with target tracking overlay.

measurement was used to quantify any fatigue effects. To measure MVC, the fingers were extended approximately 40° from full flexion, roughly midway through normal range of motion. Participants were then given three opportunities to produce maximum flexion torque. The experimenter gave oral instructions on when to contract and relax. The process was then repeated for extension torque. Average torque was calculated over a half-second sliding window and the maximum value was selected as MVC.

Participants were asked to perform a tracking task in which they were presented with a blue circle on a monitor that moved up with finger extension and down with flexion (Fig. II.1B). A white circle, representing the tracking target, moved up and down in a complex, pseudo-random pattern (Fig. II.1C). Six composite waveforms were created by summing three sinusoids at frequencies of 0.145, 0.253, and 0.274 Hertz, in which the frequencies were varied slightly to produce similar but unique waveforms. The waveforms were scaled to match the finger range of motion (0-80°). Each session consisted of six blocks of tracking practice, one for each of the waveforms, presented in random order. Each waveform had 50 peaks of the tracking target, defined as change in direction from extension to flexion. In each session of tracking practice, HEXORR was programmed to produce a torque bias against either the EDC or FDS muscle by producing 5% of the muscle's MVC in the direction opposite to the muscle's natural movement, e.g. for the extension-resisted task, a flexion torque equivalent to 5% of EDC MVC was applied throughout the practice session (Fig II.1B). In the extension-resisted task, the EDC acted as the agonist while the FDS acted as the antagonist and vice-versa for the flexion-resisted task. Because of the force applied during practice, the participant was required to use both concentric and eccentric contractions of the agonist muscle to control the movement of the cursor. As will be elaborated in the results section, the opposing muscle was still active but served as a stabilizing co-contractor rather than a movement agonist. Participants were randomized to receive either the flexion- or extension-resisted task practice in the first session to remove order effects. Before beginning each session, the participant was given thirty seconds to move freely in and familiarize him/herself with the device. Participants were then instructed to extend and flex their fingers to follow the target circle as closely as possible. They were also informed that the thumb component would follow their finger movements automatically.

Data Analysis:

In post-processing, the EMG during MVC was calculated as the maximum root mean square (RMS) of the EMG activity measured by a half-second sliding window. Activation during practice was calculated as the RMS of the EMG activity during the entire trial and normalized to the EMG during MVC. Tracking accuracy was calculated by normalizing the RMS error to the RMS error of leaving the hand closed for the entire block and subtracting this error from 1; thus 0% accuracy represents no tracking and 100% accuracy represents perfect tracking. Adaptation to practice was measured as the slope of the accuracy measurement over the six blocks of practice. Pre and post training

MVC measurements were compared with a Student's paired t-test to test for fatigue (alpha=0.05).

Each subject's RC was normalized to the average pre-training response at 150% RMT for each session. The slope of the RC was taken as a measure of corticospinal excitability (CE; Capaday et al. 1999). SICI was calculated as percent inhibition by comparing the average conditioned (paired-pulse) to the unconditioned (single-pulse) MEP amplitude (100%*(Unconditioned-Conditioned)/Unconditioned; Kujirai et al. 1993).

In the primary statistical analysis, a two-way repeated measures analysis of variance (RM ANOVA) with factors Muscle Action (agonist or antagonist) and Time (pre or post) was used to test for differences in CE and SICI of the EDC and FDS. In a secondary analysis, between-muscle effects were tested by performing a RM ANOVA on the percent change in CE (100%*(Pre CE-Post CE)/Pre CE) or difference in SICI (percent inhibition post - percent inhibition pre) with muscle action (agonist or antagonist) and muscle (EDC or FDS) as factors. The stability of unconditioned MEP amplitudes from pre- to post-training was compared using Student's paired t-test.

D. *Results*

All participants tolerated the repetitive task practice and testing sessions well and completed the study. Accuracy for flexion-resisted and extension-resisted tracking was similar: average accuracy with flexion resistance was 89.5 ± 0.4% and average accuracy with extension resistance was 89.2 ± 0.7%. A sample of the target trajectory and one subject's tracking trajectory can be found in Fig. II.1C. Participant accuracy improved with practice, measured as the slope of the accuracy measurement over the six blocks of practice. The slope of improvement tended to be slightly steeper for the extension-resisted session but was not significantly different between the two types of practice (t-value=-1.91, $p=0.088$). To ensure there was no carry-over from the first session to the second, we compared mean accuracy of the first practice block of session 1 vs. session 2 and found no significant difference ($p>0.10$). To verify that each task was targeting the appropriate muscle, we examined average activation normalized to each subject's EMG during MVC. As expected, both muscles were active in both tasks; however, muscle activation was significantly higher (approximately double) when the muscle was acting as an agonist rather than an antagonist (t-value=-6.56, $p<0.001$ and t-value=2.97, $p<0.05$ for EDC and FDS, respectively). Average activation for the EDC was 15.5 ± 1.8% of EMG during MVC while acting as an antagonist (flexion-resisted task) and 32.9 ± 0.7% while acting as an agonist (extension-resisted task). FDS activation followed a similar pattern: as an antagonist (extension-resisted task), average activation was 7.4 ± 0.6%, whereas average activation was 12.1 ± 0.6% while acting as an agonist (flexion-resisted task). This activation pattern supports the theory that one muscle is acting as the prime mover throughout the task while the opposing muscle acts as a stabilizer. Paired t-tests comparing torque produced during MVC pre- vs. post-training showed no significant muscle fatigue in either muscle for either task (p>0.10).

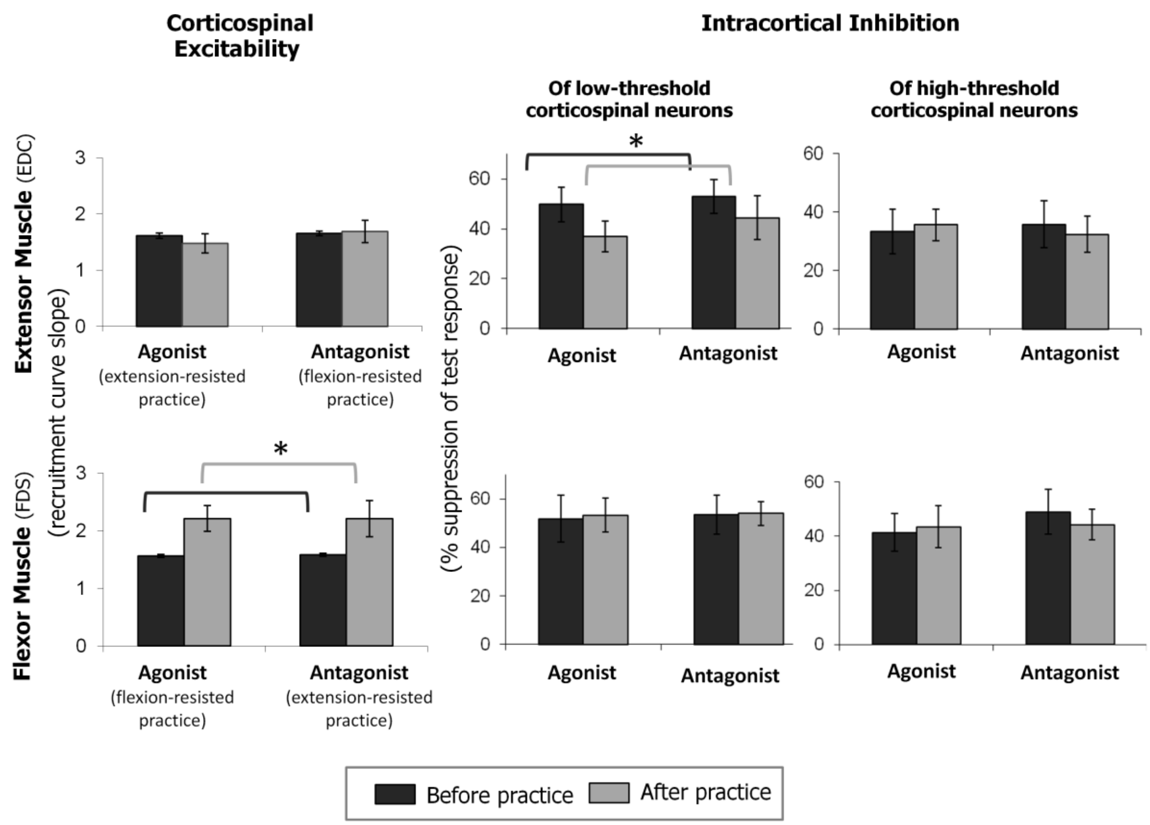

Fig. II.2: Cortical physiology in EDC (extensor digitorum communis, top) and FDS (flexor digitorum superficialis, bottom) before and after practice as task agonist vs. antagonist. Corticospinal excitability, quantified as slope of the recruitment curve, is on the left. The center and right columns represent intracortical inhibition of low-threshold (center) and high-threshold (right) corticospinal output neurons. Error bars indicate standard error.

EDC response to practice:

The primary, within-muscle, analysis tested for differences in the physiological response to the 2 types of tracking practice. In the EDC there was a significant main effect of Time (f-value=5.83, $p<0.05$) in $SICI_L$ (Fig. II.2), indicating a significant decrease in inhibition after practice regardless of the muscle's primary action as agonist or antagonist. $SICI_L$ in the EDC decreased from 49.8 ± 21.7% pre- to 36.9 ± 28.2% post-training, when acting as an agonist and from 53.0 ± 21.8% pre- to 44.5 ± 19.4% post-training, as an antagonist. There was no significant effect of Muscle Action or Action x Time interaction effect for

Table II.1: Mean and standard error of MEP amplitude (in µV) in response to single (unconditioned) and paired (conditioned) pulses and the resulting measurement of intracortical inhibition (in %).

	EDC					
	Agonist			Antagonist		
	Uncond	Cond	SICI	Uncond	Cond	SICI
	$SICI_L$					
Pre	377±249	184±145	49.8±21.7	414±225	192±135	53.0±21.8
Post	324±189	195±128	36.9±28.2	411±277	210±130	44.5±19.4
	$SICI_H$					
Pre	744±383	471±281	33.4±25.2	927±419	661±517	35.8±23.8
Post	667±259	416±196	35.6±19.8	772±376	526±281	32.4±17.2
	FDS					
	Agonist			Antagonist		
	Uncond	Cond	SICI	Uncond	Cond	SICI
	$SICI_L$					
Pre	237±158	108±98	51.8±30.7	223±154	86±69	53.6±25.4
Post	258±193	99±67	53.4±21.8	444±413	217±251	54.1±15.7
	$SICI_H$					
Pre	786±575	502±506	41.4±21.9	710±357	344±210	49.0±26.0
Post	722±370	401±243	43.5±24.5	953±623	572±447	44.3±18.2

EDC $SICI_L$. There were also no significant main effects or interaction effects in EDC CE or $SICI_H$ (Fig. II.2). For $SICI_L$ and $SICI_{H,}$ no significant differences ($p>0.10$) were detected in EDC unconditioned MEP amplitudes between pre and post, indicating that the "test MEP" amplitude remained stable after practice (Table II.1).

FDS response to practice:

In the FDS, there was a main effect of Time (f-value=7.51, $p<0.05$) on CE (Fig. II.2), indicating a significant increase in CE after practice regardless of primary muscle action. FDS CE (measured as the slope of the recruitment curve) increased from 1.56 ± 0.03 to 2.21 ± 0.23 after practice as an agonist and from 1.58 ± 0.03 to 2.21 ± 0.31 after practice as an antagonist. No significant Muscle Action or Interaction effects were detected in FDS CE, and no significant Muscle Action, Time, or Interaction effects were observed in FDS $SICI_L$ or $SICI_H$. There was a significant pre-post increase (t-value=-2.39, $p<0.05$) in the unconditioned MEP amplitudes for $SICI_L$ after extension-resisted practice. This increase in unconditioned MEP amplitude is likely related to the overall increase in CE seen in the FDS after practice. Higher unconditioned MEP values can result in higher SICI measurements (Daskalakis et al. 2002); however, since no such increase in FDS $SICI_L$ was observed, this phenomenon does not appear to have occurred under the present conditions. No other significant differences in unconditioned MEPs were observed between conditions.

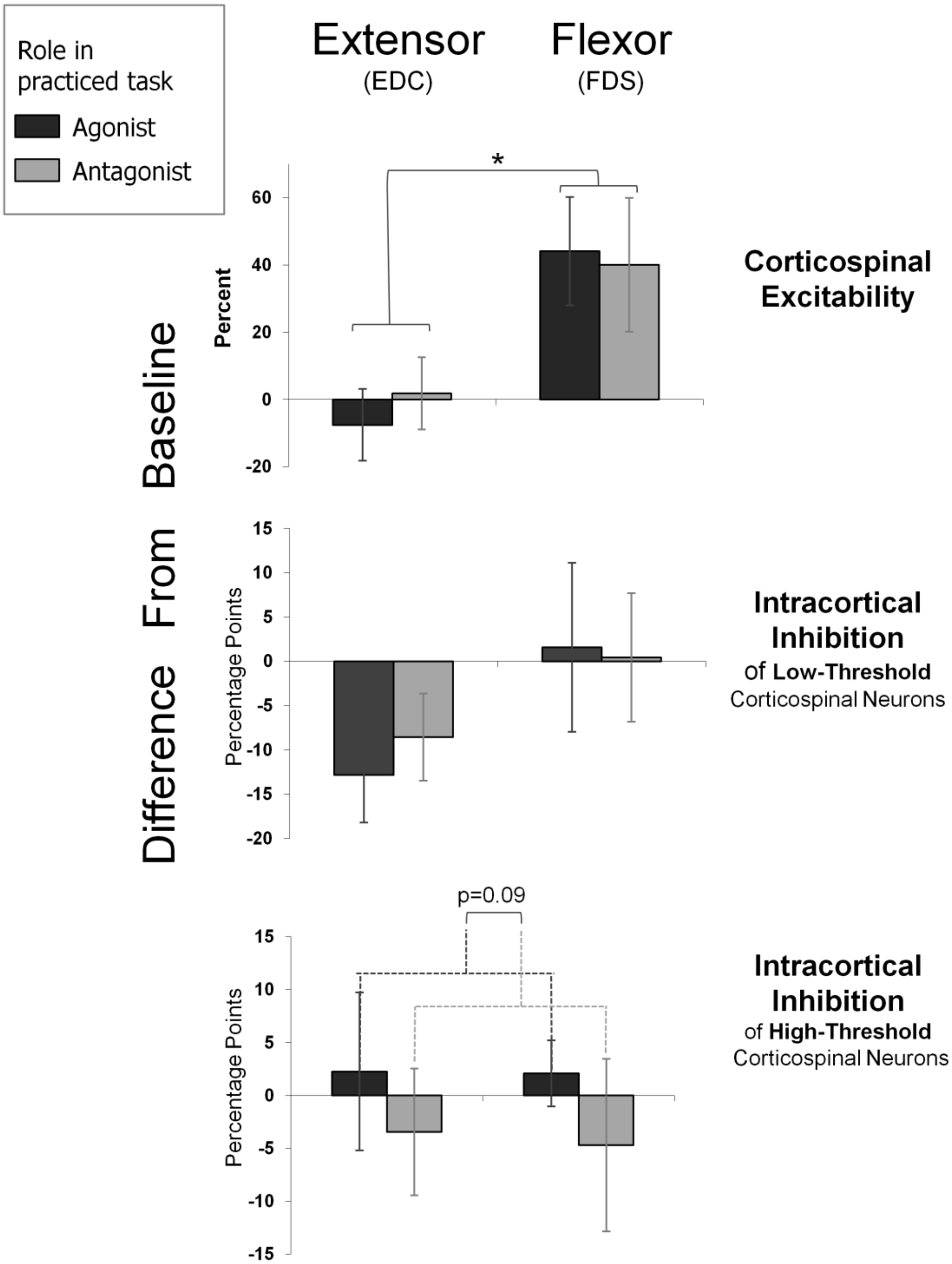

Fig. II.3: Practice-related changes in cortical physiology, quantified as percent change in CE (top) and percentage point difference in intracortical inhibition targeting low-threshold (middle) and high-threshold (bottom) corticospinal output neurons, for EDC and FDS after agonist and antagonist training. Error bars indicate standard error.

Between-muscle comparison:

The secondary analysis examined between-muscle differences in physiological response to each type of practice (Fig. II.3). Dependent variables were percent change in CE and difference in SICI percentage points from pre- to post-training. For percent change in CE, there was a significant main effect of Muscle (f-value=5.85, $p<0.05$), indicating a significant difference between the increase in CE seen in the FDS and the lack of change in CE found in the EDC. No significant Muscle Action (agonist or antagonist) or Interaction effects were detected for the change in CE. For change in $SICI_{L,}$ no significant Muscle, Muscle Action, or Interaction effects were observed. For change in $SICI_{H,}$ there was a trend (f-value=4.29, $p<0.1$) toward a main effect of Muscle Action. In both muscles, $SICI_H$ tended to increase after practice as a motor agonist and decrease after practice as an antagonist. No other Muscle or Interaction effects were observed for change in $SICI_H$.

E. *Discussion*

There has been a substantial amount of investigation into the cortical effects of motor practice, yet much of this effort has been focused on intrinsic hand muscles with little emphasis on the type of muscle (e.g. flexor vs. extensor) or its specific role in the practiced task (e.g. agonist vs. antagonist). This study is among the first to report the cortical effects of motor practice in upper extremity flexor and extensor muscles performing an equivalent task, and acting as either agonist or antagonist to the practiced task. The novel findings are that the physiological effects of motor practice can differ between flexor vs. extensor muscles and may also differ based on the specific muscle action (agonist or antagonist) required in the practiced task. After practice, there was a decrease in intracortical inhibition of the lower threshold corticospinal neurons ($SICI_L$) in EDC, the finger extensor muscle, and an increase in corticospinal excitability in FDS, the finger flexor muscle. Also, irrespective of muscle, there was a tendency toward increased intracortical inhibition of the higher threshold corticospinal neurons ($SICI_H$) after practice as an agonist and decreased $SICI_H$ after practice as an antagonist.

Practice-Dependent Plasticity

Previous studies of the cortical effects of motor practice have demonstrated the rapid changes in cortical physiology that can occur with repetitive practice, including modulation of corticospinal excitability, intracortical inhibition, and the representational area of the trained muscles. Specifically, increased corticospinal excitability and decreased SICI are often reported after a bout of motor practice (e.g. Classen et al. 1998; Liepert et al. 1998; Butefisch et al. 2000; Muellbacher et al. 2001; Garry et al. 2004; Perez et al. 2004; Ackerley et al. 2007, 2011). However, in some cases motor practice has been reported to produce the opposite effects, decreased corticospinal excitability and/or increased SICI (e.g. Teo et al. 2012; McDonnell & Ridding 2006; Classen et al. 1998;

Liepert et al. 1998). The specific training parameters that could influence these different physiological effects are not clear. McDonnell and Ridding (2006) have suggested that different patterns of practice-induced cortical modulation may be related to the type and complexity of the motor practice. Put another way, the cortical-modulation patterns that occur with motor practice may be determined by what the system must “learn” in order to improve performance. Task practice during which the individual acquires the ability to, for example, produce higher forces or faster movements could produce a pattern of cortical modulation that differs from tasks that require smaller, more precise force modulations or more complex inter-muscular coordination (such as that used in the present study).

An additional factor that is likely to modulate the cortical effects of practice is the muscles involved and their functional role in the practiced task. We examined the possible role of the type of muscle involved (flexor vs. extensor) and its action in the practiced task (agonist vs. antagonist) on practice-induced cortical modulation. Using robotics, we were able to create a task in which a flexor or extensor muscle could act as either the agonist or antagonist to the task, depending on the direction of resistance applied by the robot.

Practice effects in flexor vs. extensor muscles

The results showed that motor practice resulted in different physiological effects in a finger flexor compared to extensor muscle. In the finger extensor muscle (EDC), there was a significant practice-related decrease in intracortical inhibition of the lower threshold corticospinal neurons that did not occur in the flexor muscle. However, there was an increase in corticospinal excitability of the flexor muscle, the flexor digitorum superficialis (FDS) that was not detected in the EDC. Hence, there appeared to be a difference between the two muscles with regard to the neural circuits that were modulated in response to practice. It is possible that this difference is related to the flexor vs. extensor role of each muscle. Previous studies of upper extremity flexor and extensor muscles have reported differences in cortical projections (Palmer and Ashby 1992) as well as physiological responses to motor task demands (e.g. Chye et al. 2010; Martin et al. 2006; Z'Graggen et al. 2009).

Practice effects in agonist vs. antagonist muscle

In addition to comparing muscles that produce flexion vs. extension movements of the joint, we also compared the cortical effects of the same muscle acting as either the agonist or antagonist to the practiced task. We observed a trend toward a main effect of action, such that intracortical inhibition of the higher threshold corticospinal neurons ($SICI_H$) tended to increase when the muscle was acting as an agonist and decrease when it acted as an antagonist. Akin to the size principle in motor unit recruitment (smaller, lower-threshold neurons are recruited first; Milner-Brown et al. 1973), the higher-threshold corticospinal neurons should be activated only when more forceful muscle contractions are required. Therefore, the tendency for $SICI_H$ to increase after task practice in which a muscle acts as an agonist raises the possibility that modulation of $SICI_H$ could provide a mechanism for limiting the involvement of these higher-threshold motoneurons in order to produce smaller, more precise changes in muscle force, such as those required for the task studied here.

It should be noted that the higher test stimulus used in the measurement of $SICI_H$ recruits both lower- and higher-threshold corticospinal neurons. Therefore, the measurement of $SICI_H$ will include any effect of $SICI_L$ as well. Since $SICI_L$ decreased after practice in the EDC and was unchanged in the FDS, the trends observed in $SICI_H$ (a tendency to increase after practice as agonist and decrease after practice as antagonist) were unlikely to have been driven by $SICI_L$.

In contrast to our findings in the EDC, a number of studies have reported practice-induced modulation of corticospinal excitability in the cortical representation of an agonist but not antagonist muscle for a practiced task (e.g. Duque et al. 2008; MacKinnon & Rothwell 2000; Levenez et al. 2008). It may seem surprising, then, that no practice-induced change in corticospinal excitability of the EDC was observed in the present study; and that changes in this parameter were only observed in the FDS. The reasons for this discrepancy are not immediately obvious, but are likely to be related to specific parameters of the practiced task. For example, the level of movement precision required: Ackerley et al. (2011) found increased CE in the agonist wrist extensors following repetitive, externally-paced wrist extension practice with no change in excitability of the antagonist, but this is a much simpler task than the visuomotor tracking task used in the present study. Similarly, the function of the muscle (as a wrist instead of a finger extensor, for example) may be a factor: Chye et al. (2010) found a more prominent increase in excitability of the wrist extensors than flexors during active movement. Finally, the specificity of the muscle action (as agonist or antagonist) may also be influencing results: for example, Pascual-Leone et al. (1995) found increased corticospinal excitability in both muscle finger flexors and extensors following five days of keyboard practice in which the both muscle groups alternately acted as the agonist. Interestingly though, Smyth et al. (2010) reported a pattern of practice-related plasticity in wrist extensor muscles that is similar to that reported here after practice of a waveform tracking task very similar to that used in the present study. Emphasizing again the likely role of the type of practiced task in the physiological changes observed.

Intracortical inhibition of lower- and higher-threshold corticospinal neurons

A number of parameters can be modulated in the testing of short-interval intracortical inhibition (SICI) using paired-pulse TMS, including the interstimulus interval and the intensity of the conditioning and/or test stimuli. Often, the conditioning pulse intensity is varied in order to determine the threshold intensity at which SICI can be elicited, which can be considered a marker for the excitability of the inhibitory interneurons that mediate SICI (Kujirai et al. 1993; Kossey et al. 2003). Instead, we chose to vary the test pulse intensity while keeping the conditioning pulse intensity constant. In this way we were able to examine the effect of the inhibition elicited by the conditioning pulse on the response elicited by a test pulse that activated lower- or higher-threshold (20% and 50% above resting motor threshold, respectively) corticospinal neurons. Since the amount of SICI recorded can vary based on the amplitude of the MEP elicited by the test pulse (Daskalakis et al. 2002), we did not directly compare $SICI_L$ to $SICI_H$ but only examined the change in each parameter with practice. Interestingly, $SICI_L$ and $SICI_H$ appear to have varied differently as a function of task and muscle. $SICI_L$ but not $SICI_H$ decreased after practice in the EDC; and $SICI_H$ tended to vary based on whether either muscle acted as agonist or antagonist in the practiced task while no such tendency was observed in $SICI_L$.

<u>Use of TMS and robotics to inform stroke rehabilitation</u>

The flexibility of robotic training, in terms of the direction, type and amount of resistance (or assistance) provided, allows the physiological effects of specific training parameters to be assessed (e.g. Kamibayashi et al. 2009). This information is relevant both for our understanding of motor learning processes in healthy individuals and for principled selection of training parameters in stroke rehabilitation. For example, if we know that practicing this waveform tracking task results in decreased intracortical inhibition of the finger extensors, we may want to apply this type of training in a stroke patient who has abnormally high intracortical inhibition of the finger extensors. This also highlights the need for a better understanding of the physiological effects of stroke and their relationship to the motor impairments exhibited.

Limitations and Future Directions

One potential confounding factor is the difference in the overall amount of torque that had to be resisted by the finger flexor vs. extensor muscle during practice. The torque bias against the flexor and extensor muscles was equivalent in terms of percentage of torque produced during MVC (5%), but the peak torque of the flexors is substantially higher than that of the extensors. Therefore, the flexors had to produce higher forces than the extensors in order to accurately perform the tracking movement. Future studies should consider employing conditions in which not only the relative, but also the absolute force is matched for flexors and extensors. In the present study, though MVC differs between flexors and extensors, both resistance levels applied during practice were low and did not induce measurable muscle fatigue.

Another limitation is that the reported results occurred after only a single-session of practice, and the effects of longer-term training could differ. Interestingly, in stroke patients, Koski et al. (2004) showed a high correlation between changes in physiological measurements after single sessions of a rehabilitation treatment and the long-term therapeutic outcome that occurred with that treatment. This presents the possibility that cortical physiological responses to a single session of practice could predict the success or failure of a longer period of training. Nevertheless, future studies are needed to verify the physiological and behavioral effects associated with longer-term practice of the task used here.

Finally, the present study was performed in healthy volunteers and thus the results cannot necessarily be extended to individuals with stroke. One important consideration in translating these findings to stroke is that lesion location (e.g. cortical or subcortical) can have differing effects on cortical physiology and its practice-related modulation in individuals with stroke (Renner et al. 2009). In addition, since presumably training parameters that could produce increased inhibition of the flexors (which are often spastic after stroke) and/or increased CE of the extensors (which are often weak after stroke) would be desirable, further investigation of the physiological effects of other task parameter manipulations may be useful.

F. *Summary and Conclusions*

We conclude that practice-induced plasticity can differ depending on the muscle group(s) involved in the task and that part of this difference may relate to the type of movement the muscle produces at the joint (e.g. flexion vs. extension). It also appears that certain physiological parameters are modulated in relation to one aspect of the practiced task, such as the muscle's role as task agonist or antagonist, while changes in other parameters may be related to other aspects of the task such as the amount of force, speed or precision required. An understanding of the effects of specific task parameters on specific physiological processes has important implications for the development of more effective and individualized rehabilitation strategies for individuals with stroke.

III. THESIS AIM II: EVALUATE HEXORR TONE ASSISTANCE MODE

Portions of the following chapter were published in Conference Proceedings IEEE Engineering in Medicine Biology Society 2011; 2011:8535-8 under the title "Comparison of Tone compensation and Spring assistance for hand rehabilitation in HEXORR" © 2011 IEEE.

A. *Chapter Summary*

Robotic rehabilitation techniques have the capacity to provide high dosage therapy without the labor burden of conventional methods. The most effective means of using robots to retrain function is not yet known, though many studies now support providing assistance to movement while the user actively participates in that movement. In this study, we compare, in six chronic stroke subjects, a novel Tone assistance mode to a Spring assistance method commonly used in other robots. The Tone mode provides assistance comparable to the subject's own resistance to extension while Spring mode provides a spring-like force to pull the subject to the target. We also tested the use of a delayed assistance protocol. All subjects produced larger finger movements with robotic assistance, but all but one also produced significantly greater positive work with the Tone assistance compared to the Spring assistance. This demonstrates that subjects were actively driving the movements in Tone mode to a greater extent than in Spring mode.

TABLE III.1
SUBJECT DEMOGRAPHICS

Subject	Age	Years Post CVA	Sex	F-M (66)
S1	66	3.5	M	37
S2	35	5	F	37
S3	24	1.5	M	23
S4	49	4	M	15
S5	66	5	M	27
S6	56	9	M	19
S7	54	1	M	N/A

With Tone assistance, subjects produced movement and torque profiles more similar to that of Unassisted movement than Spring-assisted movement for fingers. These results suggest that providing assistance tailored to the user's own tone profile may be an effective means of enhancing range of motion to ultimately enable gains in hand function.

B. *Introduction*

Our device, the Hand Exoskeleton Rehabilitation Robot (HEXORR), provides assistance based on the user's own physiology. To account for patient-specific resistance to extension, we developed a tone compensation algorithm (Tone). In this study, we show the results of a comparison between Tone and Spring assistance during a simple rehabilitation game. We then evaluate these methods by comparing them to an Unassisted trial of the same game. While both assistance modes adaptively adjust assistance levels to enable subjects to complete the movements in the game, we expected different levels of subject engagement in the tasks. This was evaluated by calculating the amount of positive work the subjects performed during the game. Higher levels of positive work are preferable because this indicates the subjects are actively driving the movements and not being passively moved by the robot.

C. *Materials and Methods*

Overall Study Design

The following chapter describes the results of a comparison study in which 7 chronic stroke subjects performed a block of a game with two different types of assistance (Tone and Spring) applied in two different ways (with or without delay). A Fugl-Meyer score was collected on each subject to assess overall impairment level. The mean Fugl-Meyer was 28.6 (maximum=66, a higher score is less impaired); a profile of each subject can be found in Table III.1.

Single-session Comparison Protocol

Subjects operated under three different modes in the robot, two assessment measures and one game. First a stretch assessment mode slowly moved the subject's fingers and thumb (10 and 2.5°/s, respectively) through their full ROM five times. The stretch allowed us to measure the subject's tone by recording the motor output required to extend the digits of the hand. The second assessment recorded the subject's active ROM. The subject was asked to fully extend the fingers and thumb while the motors provided friction and gravity compensation for the HEXORR linkages. Each subject was given three one-minute attempts to reach maximal ROM before the robot completed the movement, if necessary. After each activity, subjects received the stretch again to relax the hand and

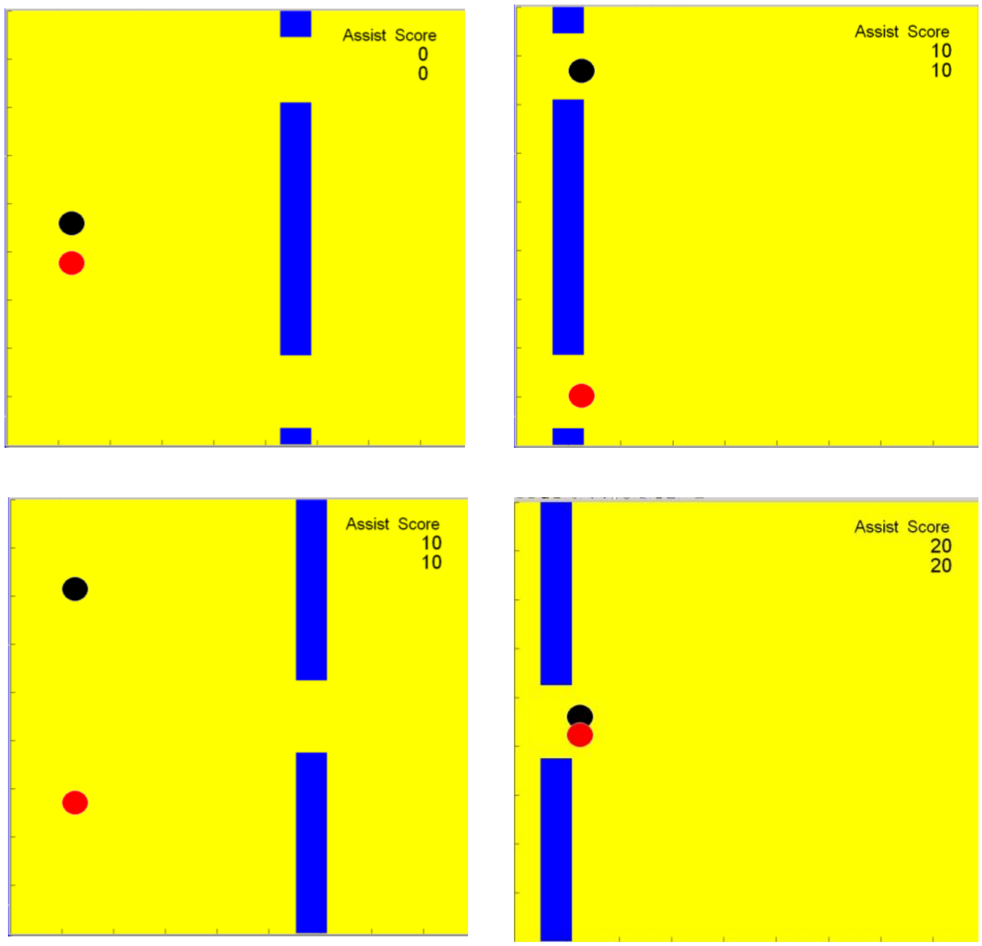

Fig. III.1: Sequence of Gate Game screenshots in extension phase (top) and flexion phase (bottom).

ensure that tone was not increasing. If the tone had increased by more than 10%, the stretch was repeated to lower the tone to previous levels. The stretch was provided a maximum of three times, after which the trial resumed regardless of tone.

The subject then played the Gate Game by using finger and thumb movement to control two balls on the screen. Figure III.1 provides a sequence of screenshots from the game: the player begins with fingers and thumb flexed and two balls in the centered on the screen. One ball (black) represents finger position and the other (red) represents thumb position. A vertical bar with two gates (extension) sweeps from the right to left on the screen. The object of the game is to move the fingers and thumb to pass the balls through the gates. The lower portion of Fig. III.1 shows the user returning to the start position by achieving a central (flexion) gate. When the player successfully passes through the gate without hitting the bar, he scores 10 points. There is no penalty for missing the gate. As a baseline measure, subjects played 3 rounds of extension and flexion gates with only friction and gravity compensation (Unassisted mode) before the assisted modes and again upon completion of the session. To test the assistance modes, each block was 30 rounds. The height of the gate was set at 200% active ROM, from the pre-test, or 85% of maximum possible ROM, whichever was lower.

Assistance Modes

We tested two types of self-adapting assistance with two application methods, assistance on during the entire extension phase or assistance during the second half of the extension phase (delay condition). For all conditions, assistance was provided only during the extension phase of the game; during the flexion phase, participants received gravity and friction compensation only. The four conditions tested were as follows: Tone, Spring, Tone with delay, and Spring with delay.

All blocks were preceded by a passive stretch trial to confirm that tone levels had not increased more than 10% of that recorded at the start of the session. Tone assistance provided extension torque to balance the measured tone during the passive stretch. Spring assistance provided a linear, spring-like force dependent on the subject's distance from the target. Initial stiffness of the Spring mode was selected so that both modes produced the same assistance level midway to the target. Thus, the average level of assistance was similar between Tone and Spring modes at the start of each block of trials.

Both types of assistance employed a self-adapting algorithm to increase or decrease assistance based on performance. Tone assistance magnitude was scaled down upon success and offset up upon failure. When the subject fell short of the gate, the offset was added to the profile at the point which the subject stopped moving. This offset method allowed the assistance profile to be shaped to match the subject's tone profile while playing. Tone decreased by 10% each time a subject successfully reached two out of two gates and was increased by an offset of 0.121 Nm as described above each time a subject failed at two out of two gates. The assistance was unchanged with one successful gate out of two. A similar algorithm was used to adapt Spring: per two gates, the assistance was decreased by 10% after two successes and increased by 10% after zero successes. Again, assistance was unchanged with only one success. Fig. III.2 shows a sample Tone and Spring assistance profile with adaptation. (Adaptation has been doubled for the sake of clarity, ie: instead of scaling down 10% it is scaled down 20% in the figure.). Note the Spring profile decreases assistance as the target is approached whereas the Tone profile increases assistance.

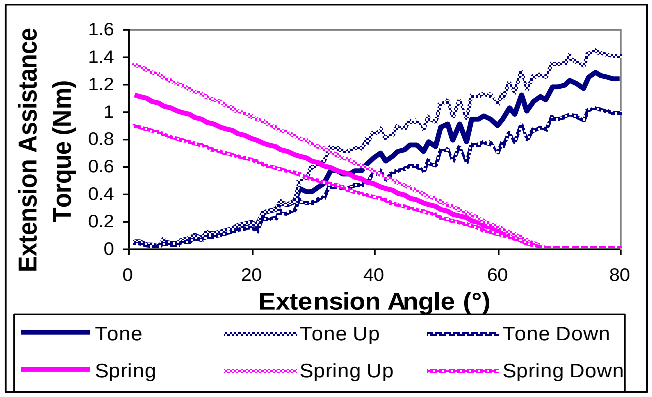

Fig. III.2. Overlay of initial and self-adapted Tone and Spring assistance profiles for S1.

<u>Data Analysis</u>

Only the fingers were analyzed. To analyze the subject's performance, extension movements in the therapy game mode were isolated from flexion movements. Flexion movements were not analyzed because assistance was only provided in extension. Work for each sample period was calculated by multiplying the distance moved (in degrees) by the average torque (in Nm) measured within the sample period. The work done over the entire movement was calculated by summing the work done in all sample periods. Positive work is produced by the user while extending; negative work is produced by the robot but may also show active braking on the part of the subject. Extension angle of the fingers goes from 0° (flexion) to 90° (extension) and refers to both the MCP and PIP angles. Delay modes were split into assisted and unassisted portions for evaluation. To enable the comparison between Delay and non-delay modes, work was normalized to displacement.

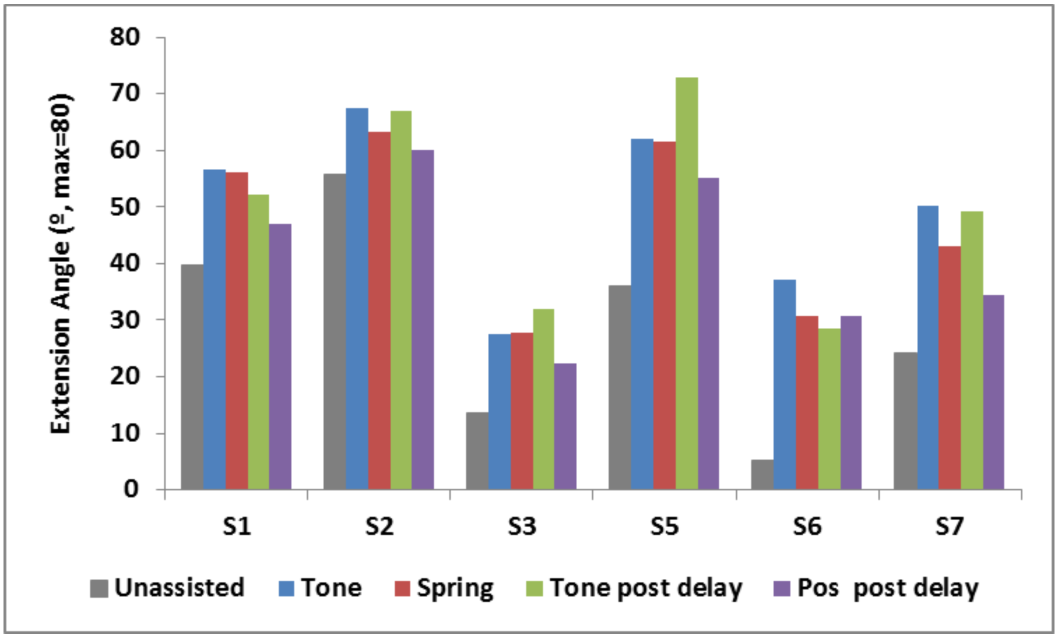

Fig. III.3. Overview of finger extension angle by subject and mode..

D. *Results*

One subject was uncomfortable in HEXORR and withdrew from the study; all other subjects tolerated HEXORR use and robotic assistance. Figure III.3 shows the average displacement for each subject. All four assisted modes enabled the user to move significantly further than achieved without assistance (p=.001, .007, .012, and .032 for Tone, Spring, Tone Delay, and Spring Delay modes, respectively). The displacement reached during the unassisted portions of the delay modes did not differ significantly from that reached in the Unassisted mode.

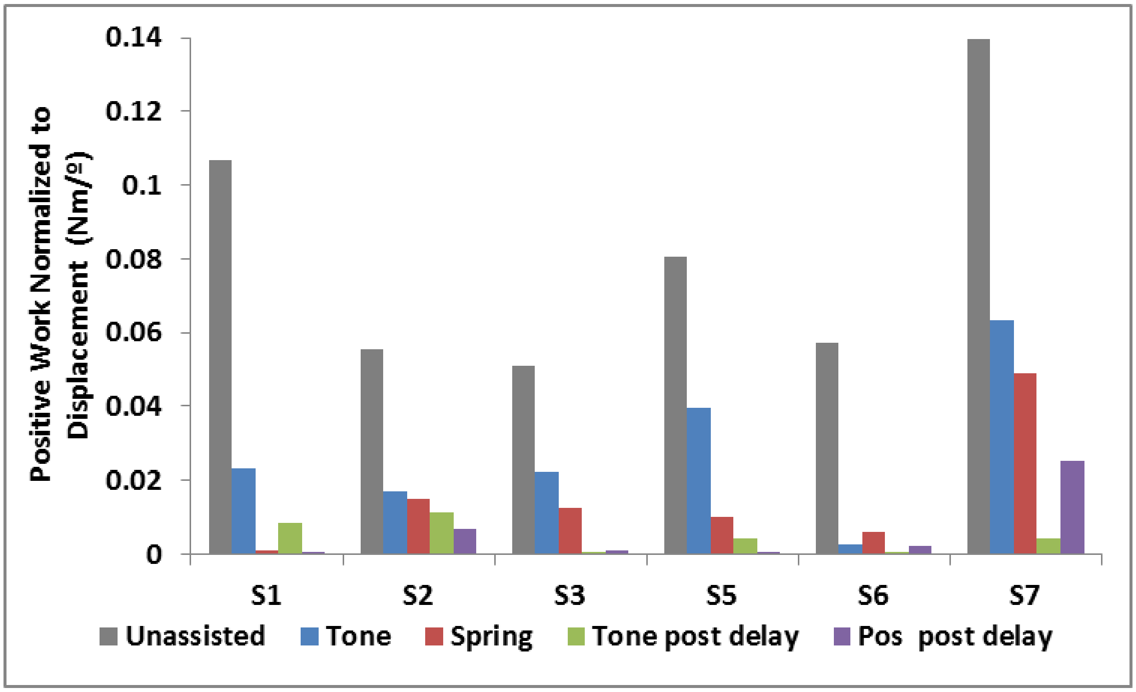

Fig. III.4: Overview of positive work by subject and mode.

Figure III.4 shows the average positive work performed during each round normalized to the average displacement of that round. Subjects performed significantly less work with assistance compared to unassisted modes (p=.002, .002, .003, and .001 for Tone, Spring, Tone Delay, and Spring Delay modes, respectively). While subjects produced more positive work overall during the delay modes (not shown), this work was largely produced during the unassisted portions of the delay modes. Subjects produced significantly more positive work during the Tone and Spring modes than during the assisted portions of Tone Delay and Spring Delay (p=.045 and .033, respectively). Negative work produced during the assisted portion of the Tone delay mode tended to be higher than Tone (p<0.10) and was significantly higher in Spring delay than Spring (p=.038). There was a trend (p<0.10) toward more subject work with Tone compared to

Spring assistance. Levels of hypertonia were also briefly examined, and five out of six subjects had maximum tone values between 0.5-0.9 Nm; S6 was a notable exception with peak tone of 1.8 Nm. S6 produced almost zero work with all assistance modes; removing him from the comparison, subjects produced significantly more work ($p=0.031$) with Tone than with Spring assistance.

To better understand the difference in positive work between the three modes, a sample extension movement from S2 in each mode was further examined. (Each sample movement was chosen because it had the largest positive work value for that mode.) Figure III.5 shows three plots overlaying displacement and torque for each sample finger movement. While both Tone and Spring modes allow S2 to achieve a larger ROM, in Tone mode the subject creates a torque profile more similar to that with the Unassisted mode. The pattern of movement is also more comparable between the Unassisted and Tone modes than the Spring mode.

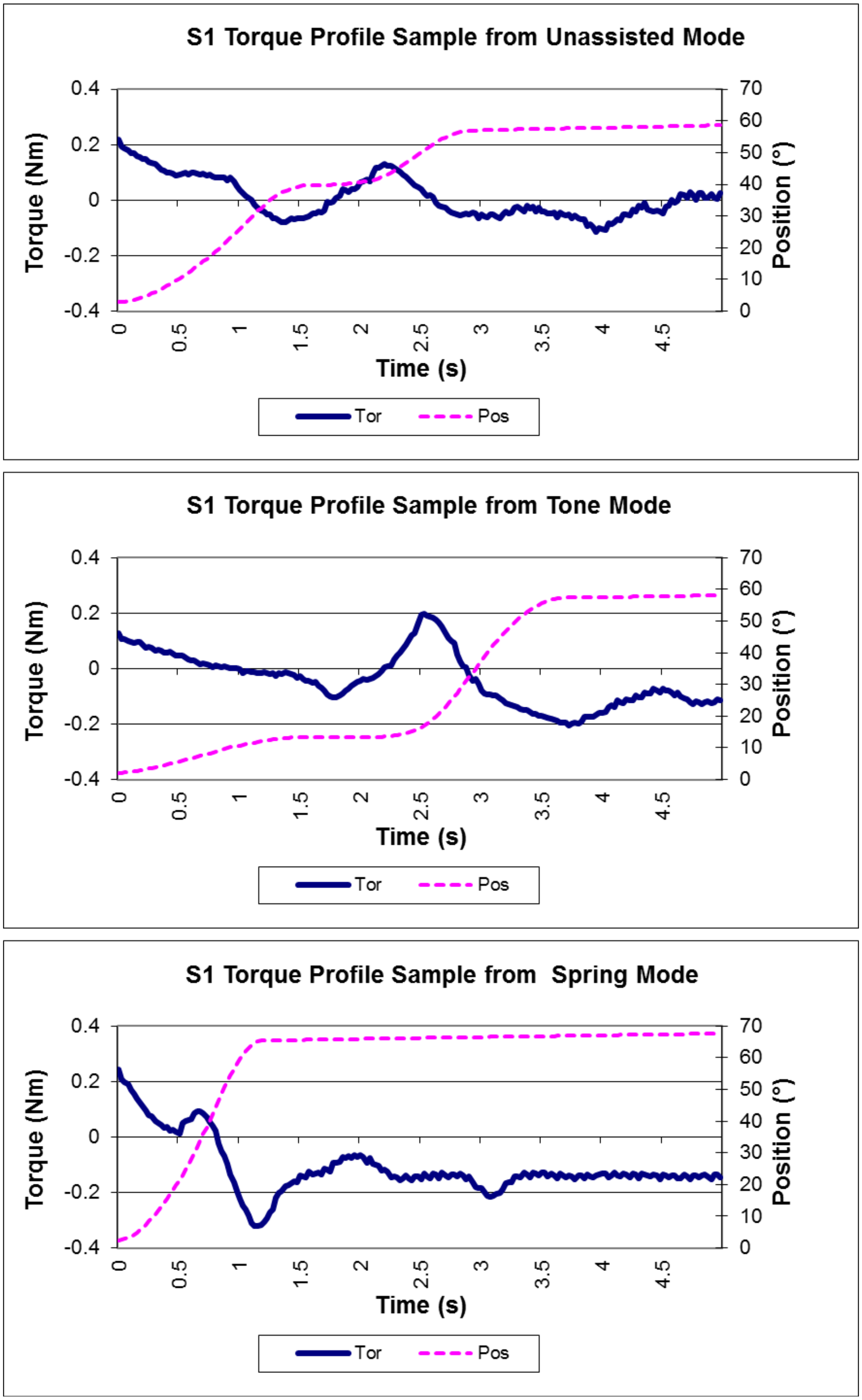

Fig. III.5: Comparison of torque and position profiles in each mode.

E. *Discussion*

The goal of providing assistance is to enable a larger ROM and therefore a larger workspace for therapeutic exercises. All four assisted modes accomplished this goal as indicated by signifcantly higher displacements. The four assisted modes differed, however, in subject work. With a delay, subjects produced less positive work and much more negative work during the assisted portion of both Tone Delay and Spring Delay modes. These data indicate subjects were largely being pulled by the robotic assistance. Also, anecdotally, subjects expressed frustration during the delay modes. Despite the higher overall positive work, the poor work values during the assisted portion combined with poor subject enjoyment suggest the Delay modes would not be beneficial in a hand rehabilitation program.

The Tone and Spring modes varied most in production of positive work. Five out of six subjects produced higher work with Tone mode. Subject 6 was the only subject to stray from this trend and produced very little positive work with either mode. He also had the highest level of impairment and the highest level of tone, which was likely a contributing factor to his performance. Related to positive work production is the torque profile subjects produce while interacting with each mode. Note the large burst in negative torque at the onset of movement in Spring mode, indicating the subject was being pulled along by the robot. In contrast, movements in Tone mode are initiated by positive torque on the part of the subject indicating the subject is driving the movements. These data suggest that while the Spring mode encourages a large ROM, it does so in a way that does not match the subject's innate movement and thus limits the subject's active participation. The lack of subject engagement indicated by the torque profile and low positive work limit the value of this mode as a method to assist rehabilitation.

The Tone mode differs from Spring primarlily in the slope of assistance: Tone assistance increases toward the target while Spring assistance decreases. In cases where hypertonia is not present, Tone and Spring assistance may be comparable methods for increasing ROM while encouraging user work. This study included subjects with flexor spasticity/hypertonia but could be adapted to those with extensor spasticity/hypertonia.

F. *Conclusions*

Subjects had much larger positive finger work with Tone and Spring than in the assisted portions of Tone Delay and Spring Delay. Subjects also performed more work with Tone assistance compared to Spring assistance while maintaining similar displacement. Similar to conventional therapy strategies in which a therapist actively assists a patient, training a larger ROM with robotic assistance may enable subjects to ultimately access that ROM outside of the robot in daily life. While both types of assistance enabled subjects to access a higher ROM, Tone assistance also enabled them to produce more work. These data suggest customizing robotic assistance to a subject's own tone profile allows subjects with hypertonia to train a wider range of motion while encouraging them to actively engage in training. In the future, we intend to expand this comparison study to include subjects from the traumatic brain injury community.

IV. THESIS AIM III: EXAMINE EFFECTS OF HEXORR TRAINING AND DETERMINE TARGET POPULATION

A. *Chapter Summary*

Robotic rehabilitation techniques show promise in rehabilitating hand function and can be used both as a tool to provide highly repetitive physical therapy and for patient assessment. A common complication of stroke is increased intrinsic resistance to hand extension due to spasticity and/or hypertonia. In this study, we present the results of seven chronic stroke subjects who completed 18 sessions of training with the Hand Exoskeleton Rehabilitation Robot (HEXORR) and pre, post, and 90-day clinical evaluations. Overall, subjects improved in both range of motion (ROM) and clinical measures. Compared to the pre evaluation, subjects significantly increased thumb ROM at the post and 90-day timepoints (mean change 7.1º and 7.0º, respectively) and middle finger ROM at the 90-day timepoint (mean change 24.7º). The largest gains were in a subgroup of 3 subjects who were less impaired at intake (higher baseline Fugl Meyer score). These subjects had significant gains in ARAT, Box and Blocks, and Grip Strength (mean changes: 4.3, 9.0, and 13.9, respectively). Future work is needed to better manage higher levels of hypertonia and provide more support to lower level subjects; however, current results support a larger, controlled trial comparing HEXORR treatment to standard of care.

B. *Introduction*

Spasticity and hypertonia often contribute to limited hand range of motion (ROM) in chronic stroke. In response to this challenge, we developed a novel tone compensation algorithm. In this paper, we will describe a preliminary clinical trial in which chronic stroke patients trained finger extension with this tone compensation and trained isometric squeezing to enhance flexor control. We evaluated hand function before and after training, and 90 days after intervention to determine the efficacy of HEXORR training, including the tone compensation algorithm, and to identify the most responsive patient population.

C. *Methods:*

Study Design:

Eight subjects with a clinical diagnosis of stroke more than 6 months prior, were enrolled in this study. All subjects were enrolled using an IRB-approved informed consent. Subject demographics and initial clinical evaluations can be found in Table IV.I. Partial data on four of these subjects has been previously presented.[15] Each subject completed

Table IV.1. Subject demographics and baseline clinical evaluation.

Subject	Sex	Age	Years Post	ARA (57)	F-M (66)	Ashworth (4)	B&B (%)	GS (%)
1	F	32	2.5	30	33	1+	9.6	24.3
2	M	60	1	31	42	0	33.3	60.0
3	M	62	25	21	23	1+	7.1	37.5
4	M	64	2.5	21	23	1+	0	38.5
6	M	26	3.5	25	26	2	3.4	7.6
7	M	65	2.5	26	34	2	9.1	23.9
8	M	24	1.5	26	23	2	3.5	51.7

ARA: Action Research Arm test; F-M: Fugl-Meyer; B&B: Box and Blocks; and GS: Grip Strength. B&B and GS are presented as a percentage of the score for the unimpaired arm.

18 training sessions of roughly 1.5 hours each. Subjects also completed a pre-training, post-training, and 90-day follow up evaluation session. Subject 3 was lost to follow up. Midway through the 18 sessions, it was discovered that subject 5 was undergoing Botox treatment, so her data was not considered in the analysis. In each session, subjects interacted with four robotic modes, two for evaluation and two for training. These modes will be described in detail in the following sections.

Evaluation Sessions:

Each evaluation session consisted of clinical measures and a ROM test. The clinical measures included the Action Research Arm test (ARA), for grasp, grip, pinch, and gross arm movement (Yozbatiran et al. 2008); the Box and Blocks (B&B), for gross manual dexterity (Desrosiers et al. 1994); the Fugl-Meyer (FM), for motor impairment (Fugl-Meyer et al. 1975); the Ashworth scale, for hypertonia of finger flexors (Gregson et al.

1999); and grip strength (GS). To test ROM, subjects donned the CyberGlove (Immersion, USA) and were asked to open and close the impaired hand repeatedly.

Tone Compensation:

The stretch mode was used to measure each user's unique resistance to movement by measuring the motor torques required to balance the digits in any posture and recording them into a posture-dependent lookup table. In the Gate Game, the HEXORR motors use the lookup tables to provide assistive torque (or tone compensation) during active extension movements. With tone compensation, only small muscle extension torques are needed to extend the digits even in subjects with high flexor tone, thus enabling subjects with extensor weakness and/or flexor tone to actively engage in extensor training. A more-detailed description of the tone compensation algorithm used in this study can be found in Godfrey et al. 2011.

The compensation can be scaled up or down to adjust the assistance level. Using guidelines described below, assistance was scaled up 5% or scaled down 10% to adjust the assistance provided to the user. After the first 5 subjects had completed the training, we modified the tone compensation to include an auto-shaping element. Assistance was decreased with a scaling factor (10%) and increased by adding an offset to the assistance curve at the point the subject was last able to reach. By shaping the assistance curve, the assistance was able to follow the real-time changes in subject's tone with greater fidelity.

The auto-shaping algorithm is described in greater detail in Lum et al (in press).

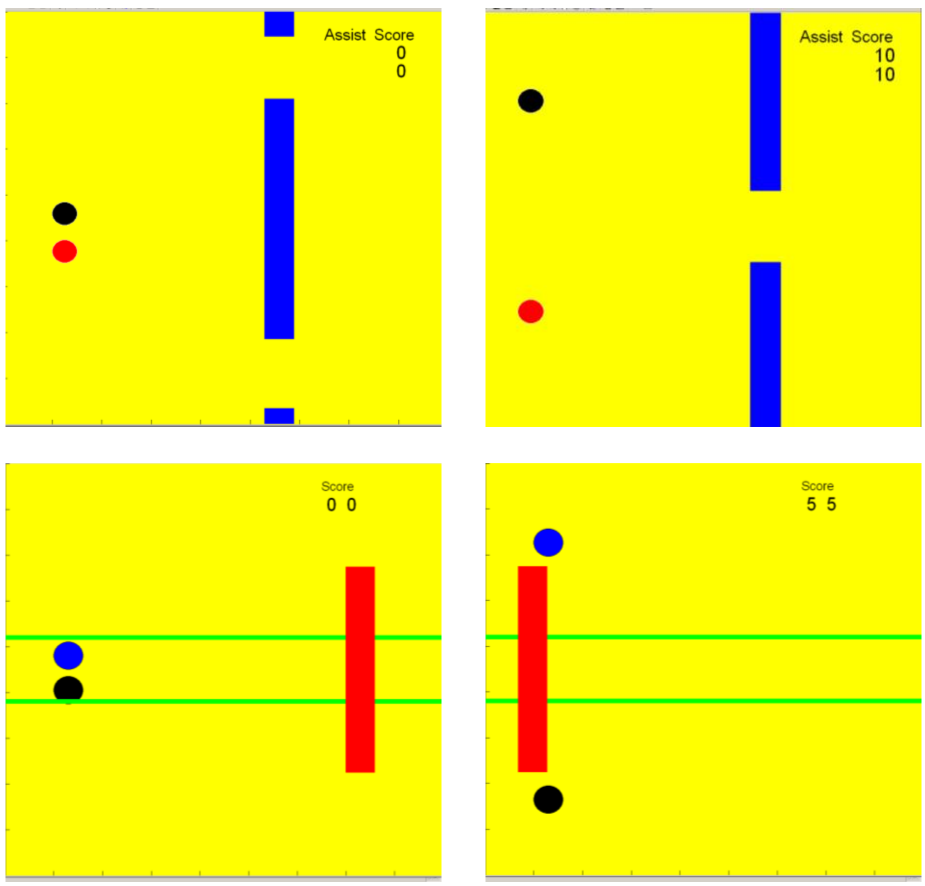

Fig. IV.1: Graphical user interface for Gate Game (top panels) and Squeeze Game (bottom panels). Top left shows the Gate Game during an extension gate. The top ball represents the finger position while the bottom represents thumb position. Top right shows a flexion gate. Bottom left shows a user producing a flexion force to maintain the balls in the channel to activate the wall, while bottom right shows a user releasing the flexion force to successfully avoid the sweeping wall. The top ball represents finger force while the bottom ball represents thumb force.

Training Protocol:

Each session began with a passive stretch of the hand. While the subject relaxed, the motors moved the fingers and thumb through the subject's passive ROM (finger MCP/PIP and thumb IP/MCP/CMC ROM) five times at a speed of 10º/second for the fingers and 2.5º/second for the thumb. The stretch allowed subjects to acclimate to the robot and provided a measure of passive resistance or tone. Subjects were then given three opportunities to open and close the fingers and thumb to determine active ROM. If desired, subjects could rest during a movement. Once maximum active ROM had been reached, the robot completed the movement to reach full extension. Subjects then played two different games for the remainder of the session. Passive stretching was repeated at the subject's request throughout the training session.

The first therapy mode was the "Gate Game," designed to train active finger extension. It required the subject to extend and flex the fingers and thumb to guide two balls through two openings in a gate that sweeps across the screen (Fig. IV.1). This game was played with assistance in the form of tone compensation. For subjects 1-5, each block consisted of 8 extension and 8 flexion gates, and settings were adjusted after each block. For later subjects, each block consisted of 25 gates; tone compensation was adjusted online every 3 gates and other settings were adjusted after each block. The Gate Game included many parameters to adjust difficulty, such as the height and width of the gate opening and the gate's speed. To keep the subject challenged and motivated, tone compensation and other parameters were adjusted after each block using the following guidelines: if the subject had a 70% or greater success rate on the extension movements, tone compensation was scaled down by 10%. If the success rate was 30% or less, tone compensation was scaled up 5%. Once tone compensation was minimized (reached near zero levels), movement length was increased and tone scaling resumed. In the highest level patients, if tone compensation had been minimized and movement length maximized, gate speed was increased and ultimately window width decreased. For the last three subjects, tone compensation scaling was automated and occurred every three repetitions. Also, to further optimize the tone compensation provided, compensation was increased when necessary using an offset rather than scaling.

The second exercise was an isometric force game, dubbed the "Squeeze Game" (Fig. IV.1), designed to train flexor relaxation and extension after active flexion. The hand was held in the middle of the passive ROM as the subject practiced flexion and relaxation. Finger and thumb flexion must be coordinated to move two balls toward the centerline of the screen, thus activating a sweeping wall. Subjects must then release this flexion force to move the balls away from the centerline and avoid collision with the sweeping wall. Each block consisted of 5 repetitions, and the daily goal for the Squeeze Game was 5 blocks for 25 repetitions per day. Several parameters were again included to adjust the game difficulty. These included the wall's speed, the precision and amount of force required (25, 50 or 75% of maximum), and the wall's height (which correlates to the degree of flexor relaxation). As in the Gate Gate, a rubric was used to move through these adjustments: with successful completion of blocks, first gate speed was increased, followed by percent relaxation required, followed by length of contraction, either an increase or decrease in required force, and finally increase in required precision of force. (Because of variation in subject's flexor control, some users were more challenged by controlling a smaller force while others with producing a greater force; the easier setting was used as a starting point.)

Data Analysis:

Subject 3 completed the training but dropped out before the 90-day follow up and Subject 5 was being treated with Botox and was excluded from analysis. Subject 8 has not completed the 90-day follow up. For ROM analysis, the fingers and thumb were separated. The IP joint was analyzed for the thumb. For the fingers, ROM at the MP and PIP joints were summated for each subject and averaged across subjects. Subject 2 was removed from analysis for the fingers because he showed full ROM (hyperextension) at the pre evaluation. His thumb data were retained in the analysis. To analyze the clinical measures, Box and Blocks and Grip Strength were calculated as a percentage of the score of the unimpaired arm on the same day. The total Fugl Meyer score as well as the hand/wrist subcomponent were analyzed. Paired t-tests were used to detect significant changes between timepoints in the measures.

D. *Results:*

Subjects trained 2 or 3 times a week depending on their availability and took on average 57±14 days to complete training, with the exception of subject 6 who experienced difficulties with transportation and took 101 days to complete training. Subjects received on average 446±219 repetitions/week (including both Gate and Squeeze Games).

Figure IV.2 shows a summary of the unassisted maximum extension ROM measured with the robot over the course of the training sessions (top, middle) as well as with the Cyberglove (bottom). Five subjects showed a positive slope indicating an increase in finger ROM over the course of the training. Subject 2 had full finger ROM in the robot at the beginning of the training and maintained this level throughout the training. Subject 6 showed little change beyond daily variation in his finger ROM in the robot. Thumb results were similar: across the 18 sessions, 5 out of 7 subjects increased their ROM in the robot. Subjects 3 and 6 showed relatively flat profiles, indicating no change in voluntary thumb extension in the robot over the course of treatment. On average, subjects showed similar gains in maximal extension when measured by the Cyberglove (Fig. IV.2, bottom). The increase in maximum thumb extension was significant at the post and 90-day timepoints ($p<0.01$ and $=0.038$ and mean change: 7.1º±4.9º and 7.0º±5.1º, respectively). The 90-day timepoint for digit 3 also showed significant improvement ($p=0.047$, mean change: 24.7º±15.1º) and digit 2 improvements approached significance at post and 90-day timepoints ($p<0.10$, mean change: 29.2º±30.6º and 22.1º±18.7º, respectively).

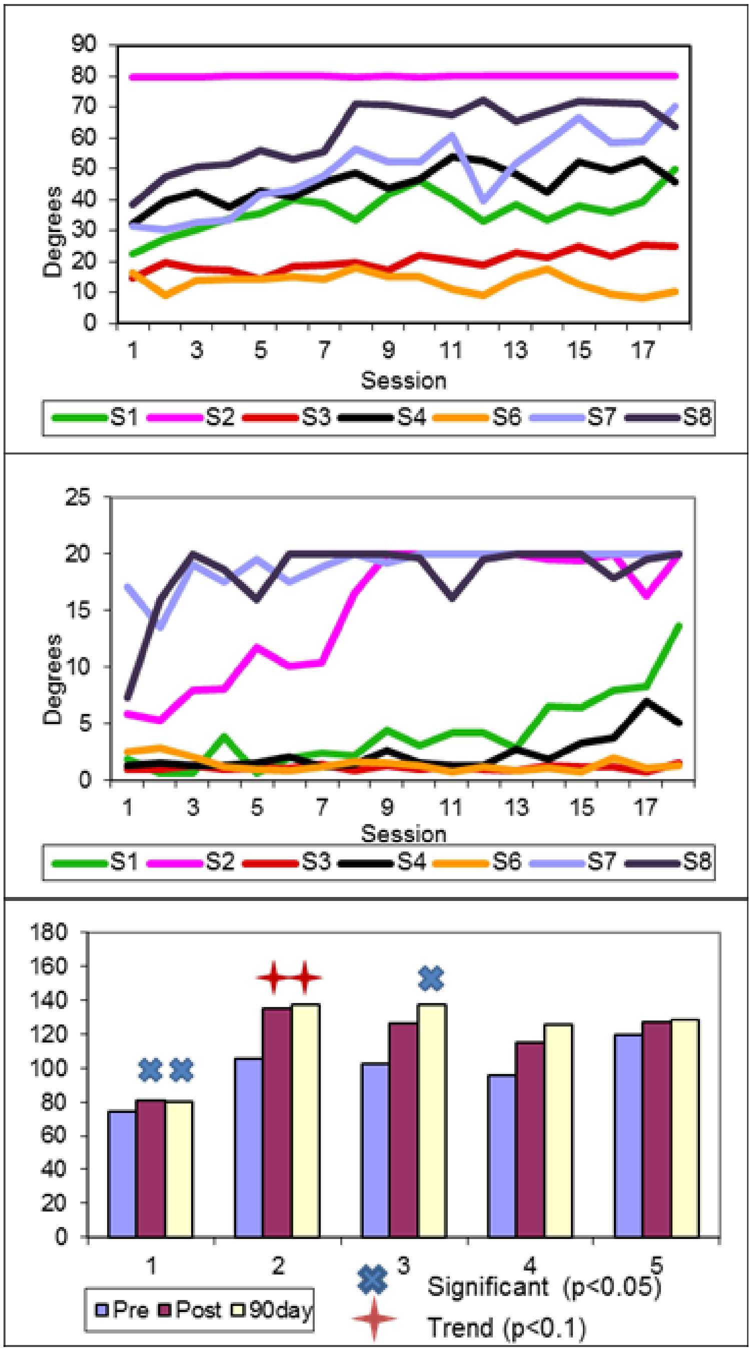

Fig. IV.2: Extension Data: The top two panels show the extension ROM achieved at each session in the robot for the fingers (top panel) and thumb (middle panel). The bottom panel shows the group average maximum extension measured outside of the robot with the Cyberglove. (Digits 2-5, the fingers, do not include data from Subject 2.) Significant changes ($p<0.05$), with respect to the pre timepoint, are marked with an asterisk. Trends ($p<0.10$), with respect to the pre timepoint, are marked with a plus sign

Analysis of clinical measures found a significant ($p<0.01$, mean change: 12.0±4.1%) increase in Grip Strength at the 90 day timepoint. The following measures approached significance ($p<0.1$): Grip Strength at the post timepoint (mean change: 9.2±10.3%), Box and Blocks at the 90-day (mean change: 5.4±5.3%), and the hand/wrist Fugl Meyer at the 90-day (mean change: 1.8±1.6).

Group clinical measures at each timepoint are summarized in Fig. IV.3. Overall improvement measures, ARAT and FM, showed little change. Subjects improved in hand-specific clinical measures such as the hand/wrist subcomponent of the Fugl-Meyer,

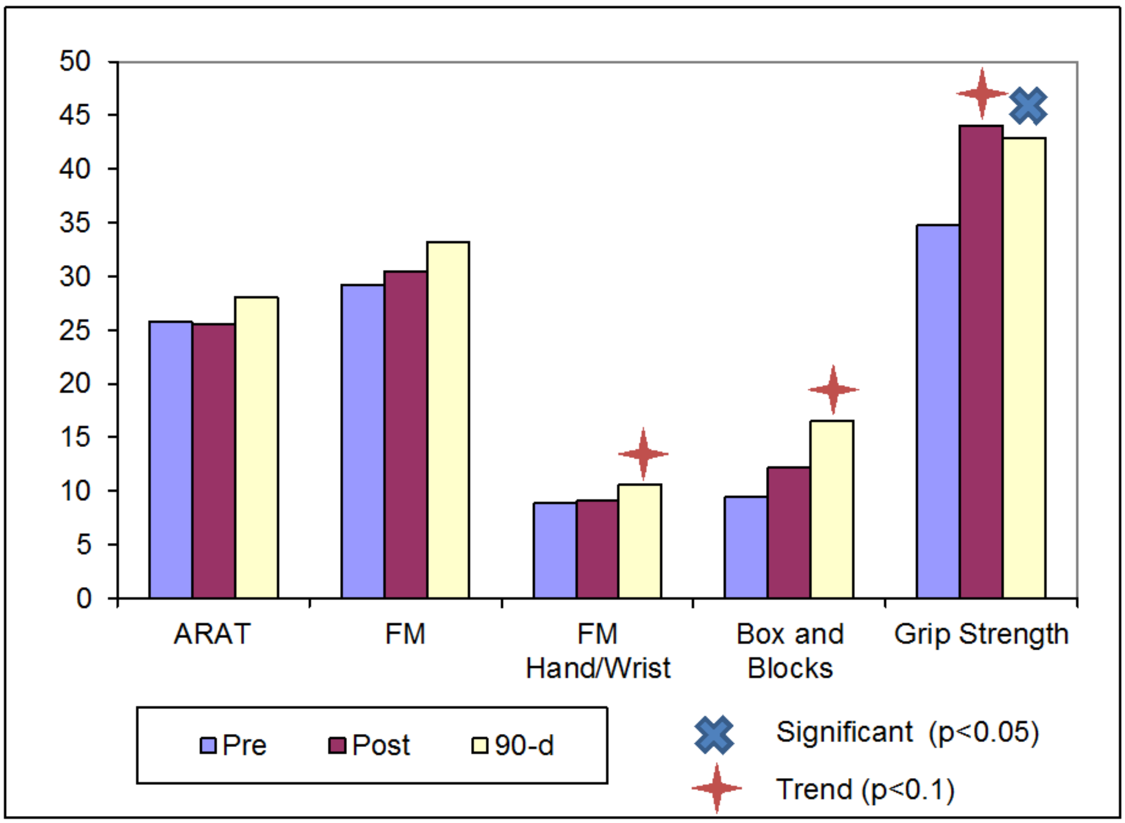

Fig. IV.3: Group average clinical measures at the pre, post, and 90-day timepoints. The blue X indicates a significant change ($p<0.05$) with respect to the pre timepoint and the red cross indicates a trend ($p<0.1$) with respect to the pre timepoint.

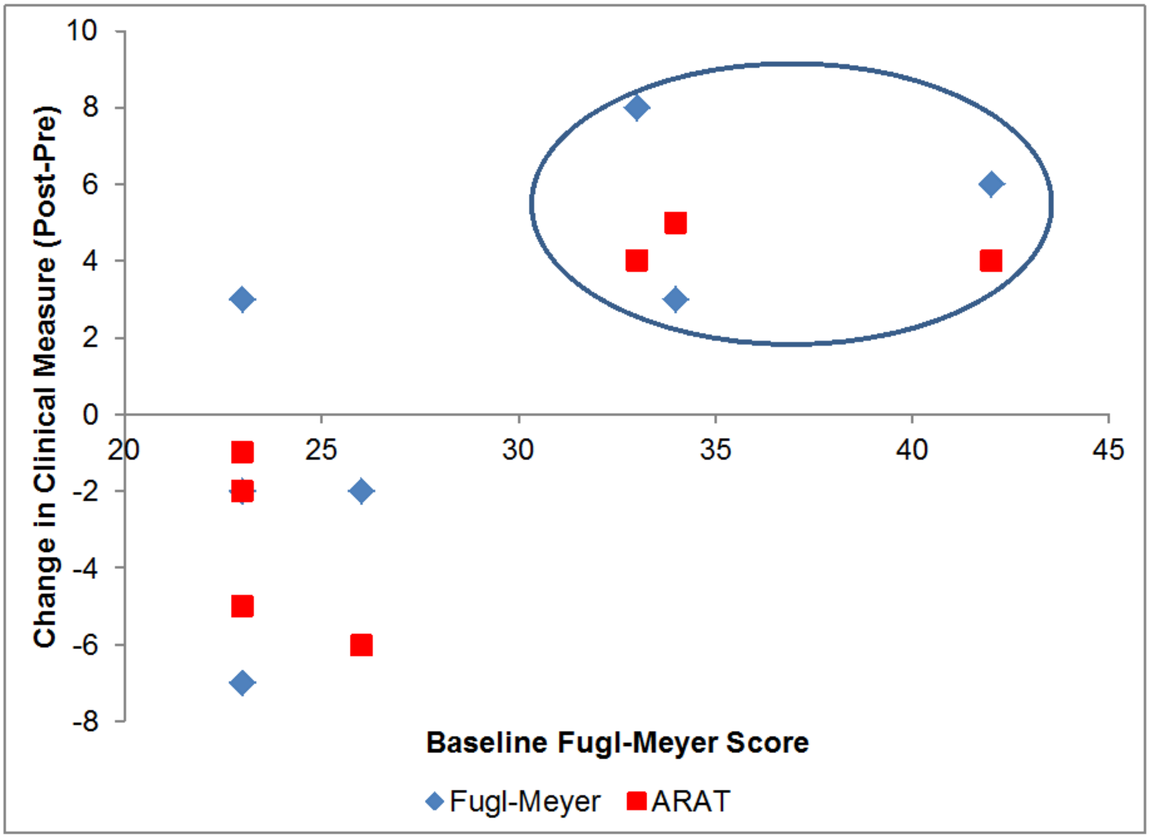

Fig. IV.4: Correlations between change in FM and ARAT and baseline FM score.

Box and Blocks, and Grip Strength. Significant changes were observed in the Grip Strength 90-day timepoint (mean change: 12.0±4.1). Trends were observed in the Grip Strength post (mean change: 9.2±10.3) as well as the 90-day hand/wrist FM and B&B timepoints (mean change: 1.8±1.6 and 5.4±5.3, respectively).

Anecdotally, subjects that were less-impaired at enrollment (high Fugl-Meyer), tended to improve more with HEXORR training. We examined this trend by comparing initial Fugl-Meyer score with change in Fugl-Meyer (pre to post) and change in ARAT (pre to post). We found a significant correlation (p=0.03) between intake FM and change in

ARAT and a trend ($p<0.1$) between intake FM and change in FM. Fig. IV.4 shows these correlations. We next examined the subset of subjects encompassed in the blue oval.

These subjects had a baseline FM score above 30 and showed more generalized improvement. The average clinical measures of this group can be found in Fig. IV.5. Significance at the 90-day timepoint of Grip Strength was retained (mean change: 13.9±4.0) as was the trend at the 90-day hand/wrist FM (mean change: 2.7±1.5). Change in Box and Blocks at the 90-day timepoint was significant ($p=0.02$, mean change

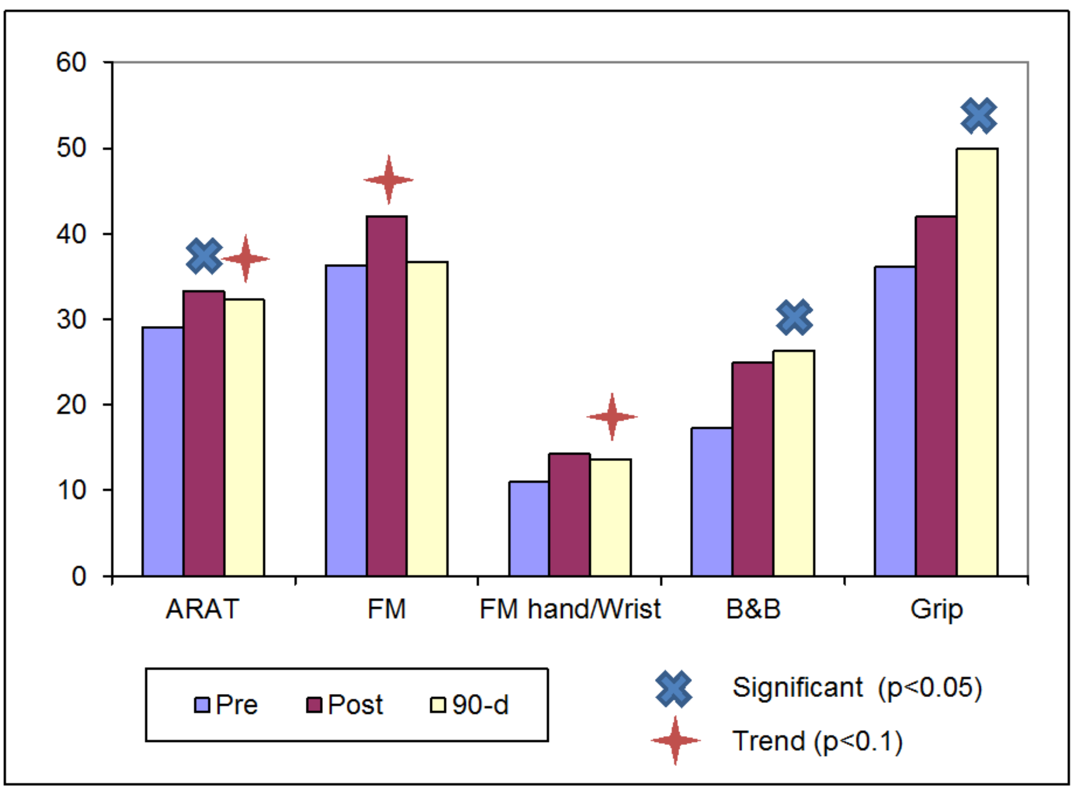

Fig. IV.5: Average values of clinical measures at the pre, post, and 90-day timepoints for the high-Fugl-Meyer subgroup. Units on the Y-axis are points for ARAT, FM, and FM hand/wrist and percentage points for B&B and GS. Significant changes ($p<0.05$), with respect to the pre timepoint, are marked with a blue X. Trends ($p<0.1$), with respect to the pre timepoint, are marked with a red cross.

Table IV.2: Comparison of Ashworth score at baseline to average peak tone during training.

	S1	S2	S3	S4	S6	S7	S8
Ashworth	1+	0	1+	1+	2	2	2
Peak Tone (Nm)	1.00	1.16	1.71	0.76	2.40	0.97	0.69

9.0±2.0). This subgroup also had significant gains in the post ARAT ($p<0.01$, mean change: 4.3±0.6) and trend in 90-day ARAT and post FM ($p<0.10$, mean change: 3.3±1.5 and 5.7±2.5, respectively).

We also examined the daily measurements of tone in HEXORR and compared them against the Ashworth score for each subject at baseline. The maximum of the average tone and the Ashworth score can be found in Table IV.2. No correlation was found between these measures suggesting a need for more objective measures of hypertonia. Higher levels of tone may also have affected the subject's ability to interact with HEXORR during the Gate Game, as will be explored in the discussion.

E. *Discussion:*

This study shows the potential benefits of intensive hand training with HEXORR and also suggests initial level of impairment is a factor that may limit these benefits. Subjects had significant increases in Grip Strength and extension of the middle finger and thumb. Box and Blocks, hand/wrist Fugl-Meyer and extension ROM of the index finger showed a tendency to increase.

HEXORR training is effective at increasing ROM and grip strength in patients with a wide range of initial impairments. These increases translate to improvements in the more hand-centric clinical measures: the Box and Blocks and hand/wrist subcomponent of the FM. However, improvement in more generalized impairment measures was only seen in the higher level subjects. The Box and Blocks test requires the subject to grasp small (approx. 1-inch cubed) blocks and transport them over a low wall and release. Similarly, the hand/wrist subcomponent of the Fugl-Meyer includes various hand and wrist postures as well as grasp ability without involving the upper extremity. In contrast, the ARAT and FM require the subject to perform proximal arm movements often in conjunction with a distal grasp. The subgroup of more impaired subjects (low FM at baseline) had very low scores (average 13.3 out of 36 possible points) in the proximal subsection of the FM at baseline. These limitations in the proximal arm likely impaired their ability to successfully complete the distal portions of the FM and ARAT. The subjects with higher FM at baseline, however, had much higher proximal scores (average 22.7 points) thus allowing gains in distal movement to translate to gains in overall FM and ARAT. To provide further functional benefit to the lower-level patients, HEXORR training could be combined with or succeeded by proximal arm training in future studies.

It is worth noting that all three subjects in the less-impaired subgroup as well as one in the more-impaired subgroup showed modest improvement in the proximal arm as seen in the shoulder/elbow subscore of the Fugl Meyer. These results suggest training the distal arm may also provide benefits to the proximal arm. Though the shoulder/elbow is not directly trained while using the robot, subjects likely engaged the proximal arm to stabilize the arm during the training. A similar effect has been seen previously where a group trained the proximal arm and showed small improvements in the hand/wrist FM (Krebs et al. 2008). Previous studies investigating the coordination of reach and grasp actions have found common neural pathways (Stark et al 2007, Cavina-Pratesi et al 2010), suggesting that training one component, such as the hand, may also strengthen another component, such as the shoulder or elbow.

One question that often arises with training studies is relevance: are the changes seen in the study clinically meaningful for the patient. For the ARAT, an MCID of 5.7 points (or 10%) has been used previously (van der Lee et al. 2001). Three subjects approached this value: S1 and S2 both increased 4 points and S7 had a gain of 5 points. On the FM, an MCID of 6.6 points (10%) was used in (Gladstone et al. 2002). At the post evaluation, S1 achieved MCID with either criteria with an increase of 8 points and S2 approached this value with a change of 6 points. For B&B and GS, we calculated each subject's performance with the impaired arm as a percentage of their unimpaired arm's performance, therefore we considered a gain of 10 percentage points the MCID. Using this criterion, S7 increased 16.4 percentage points on the B&B. S1, S6, and S8 increased 12.3, 15.4, and 27.3 percentage points, respectively, on the GS. It is also worth noting that S1 and S2 showed gains in all 4 outcome measures, although not all of these reached MCID. Overall, 4 out of 7 subjects had clinically important gains in at least one outcome measure. Improvements in outcome measures seen in this study are comparable to that of previous studies: Takahashi et al (2008) found increases of 4 points on the ARA and 7 points on the FM after use of a hand/wrist robot; Lo et al (2010) showed changes of 1.1 and 3.9 points on the FM in two groups after training for 12 weeks with an arm and hand robotic system; a review by Kwakkel et al (2008) found an overall change of 7-8% on the FM with upper limb robot-assisted therapy.

As noted above, hypertonia measured by the Ashworth scale did not correlate to robot measurements of tone. This phenomenon was likely caused both by the highly variable nature of tone as well as the challenges faced with a subjective clinical measure. It also illustrates the need for objective measures of patient impairment and progress. Subjects 3 and 6 had much greater tone than the other subjects (roughly double peak tone, in HEXORR) and spent a larger portion of training in a flexion hold phase. Stroke patients sometimes experience a flexor spasm, an involuntary increase in flexor activation, particularly during exertion. To mitigate the effects of these spasms, the robot prevents flexion movement during the extension phase of the Gate Game. If the encoder detects an inappropriate flexion movement, the robot enters a hold phase that requires an extension movement to exit the hold and resume play. To assist users in breaking out of the hold phase, the robot provides a restoring torque back to the position at which the hold was entered however tone compensation is not provided during the hold. This resulted in high tone subjects often getting stuck in the hold phase. These data suggest that the position control method employed for preventing flexion movement is inappropriate for subjects with high tone. We will address this issue by supplementing the position controller employed during the flexion hold phase with tone compensation.

Study Limitations and Future Work:

While this study highlights the benefits associated with actively retraining the stroke hand, further studies are needed to validate these results. However, evidence to date does suggest modification of the control algorithm is needed for subjects with higher tone levels. Similarly, more impaired subjects may receive greater benefits from HEXORR training if combined with proximal arm therapy. The target dosage of this study may also have been too low; Lo et al showed an intensive, robot therapy group improved significantly more usual care, however that study had a target dosage (number of repetitions) nearly 10 times greater than ours (2010). The Gate Game was designed to emphasize active finger extension while the Squeeze Game emphasized flexor relaxation. Improvement in flexor relaxation would likely have had the largest impact on the Box and Blocks outcome measure because of the requirement to grasp and then release the blocks. Four subjects showed gains in this measure, only one of which reached MCID. Future studies should also investigate the optimal dosage of each game to maximize subject gains or tailoring the dosage of each game to the subject's impairment. Also, since this study does not feature an active control group, future studies are needed to compare the benefits of HEXORR training to that of conventional therapy.

F. *Conclusions:*

The results of this study suggest HEXORR is a useful tool for retraining extension and ultimately hand function in stroke subjects, although more impaired subjects may require proximal support. The current tone assistance method works well for mild-moderately impaired subjects however adjustments are needed to benefit subjects that exhibit higher tone. These adjustments in the flexion hold phase along with the auto-shaping algorithm may allow a wider range of subjects to effectively train with HEXORR. The high-FM group of subjects showed promising gains in both range of motion and clinical evaluations and overall 4 subjects showed clinically meaningful improvement in at least one outcome measure. These results warrant further study of this robotic approach.

V. CONCLUSIONS

Each aim of this thesis makes a unique but related contribution to the field of rehabilitation. In Aim I, we identified evidence of differential motor control of finger flexors and extensors. Flexors and extensors responded differently to a motor practice task. While this research was conducted using healthy volunteers, it could be extended to the stroke population and used to establish more effective training paradigms for stroke patients. In Aim II, we established Tone compensation assistance as an effective means of increasing ROM while maintaining patient engagement and motivation. Subjects performed better with Tone compensation than with another, often-used, assistance method. The Tone compensation also allowed subjects to train a larger ROM than unassisted trials while avoiding the fatigue of training without assistance. With the final aim of this thesis, Aim III, we showed HEXORR is effective at training strength and ROM in stroke patients and produces functional gains in less-impaired patients. Together, these finding can be used to improve the paradigms used to rehabilitate stroke patients. Future work to extend the physiological findings to the stroke population and confirming the HEXORR training benefits against control therapy would further benefit the field.

VI. APPENDIX

A. *Simulink Model*

The following figure (Fig. V.1) is a screenshot of the top level of the Simulink (Mathworks, Natick) model that runs HEXORR for the comparison study presented in Chapter III. The model was adapted from the program designed by Dr. Christopher Schabowsky, one of the developers of HEXORR, to run the robot. The left-most

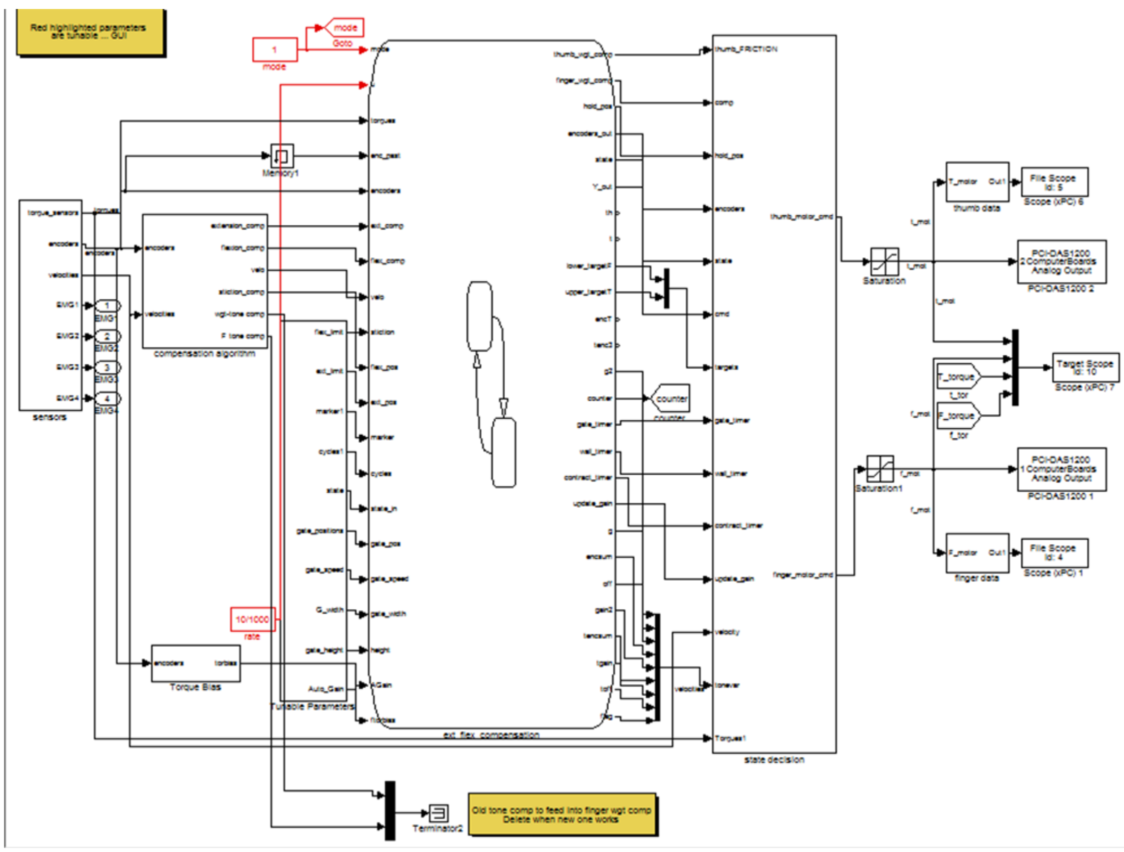

Fig. V.1: Top layer of Simulink model for comparison study presented in Chapter III.

subsystem, entitled “sensors,” converts the raw signal from the electronics box into measures of torque, position, and velocity with appropriate units. These readings are then sent into a variety of subsystems for example the “compensation algorithm” and Stateflow subsystems.

The “compensation algorithm” subsystem uses the velocity of the robot to determine the appropriate type of friction, static or dynamic. The position input determines the amount of dynamic friction, gravity compensation, and tone compensation (if appropriate). The “tunable parameters” subsystem gathers all parameters that can be set by the graphical user interface (GUI) outside of the model; these include gate height, gate speed, etc. These parameters, along with the compensation amounts, are fed into Stateflow block in the center of the figure. This block runs the modes and games with which the user interacts using logic to determine robot states. States 1 and 2 correspond to extension and flexion states, respectively, and thus include gravity and friction compensation in the appropriate direction for the intended movement. State 3 is a “hold” state and is used as a flexion catch when a user unexpectedly flexes during an extension phase and also runs when a user has reached a safety software stop. Finally, state 4 is a passive state in which the robot is driving the movement and no input from the user is required.

The “state decision” block establishes motor commands. The state, position, velocity, and other inputs are used to determine the appropriate value of motor output. This output is passed through a saturation block to protect both the user from excessive torque and the motor from burnout. This block also includes real-time calculation of positive and negative work for both finger and thumb components (Fig. V.2). A lookup table provides the position-dependent torque bias and is used to determine the torque produced to move each step. This torque is then multiplied by the encoder difference over the step to calculate the work performed at each step. The experimenter is provided both with cumulative torque over a block of exercises as well as cumulative work over each phase of exercise (for example, one extension movement in the Gate Game).

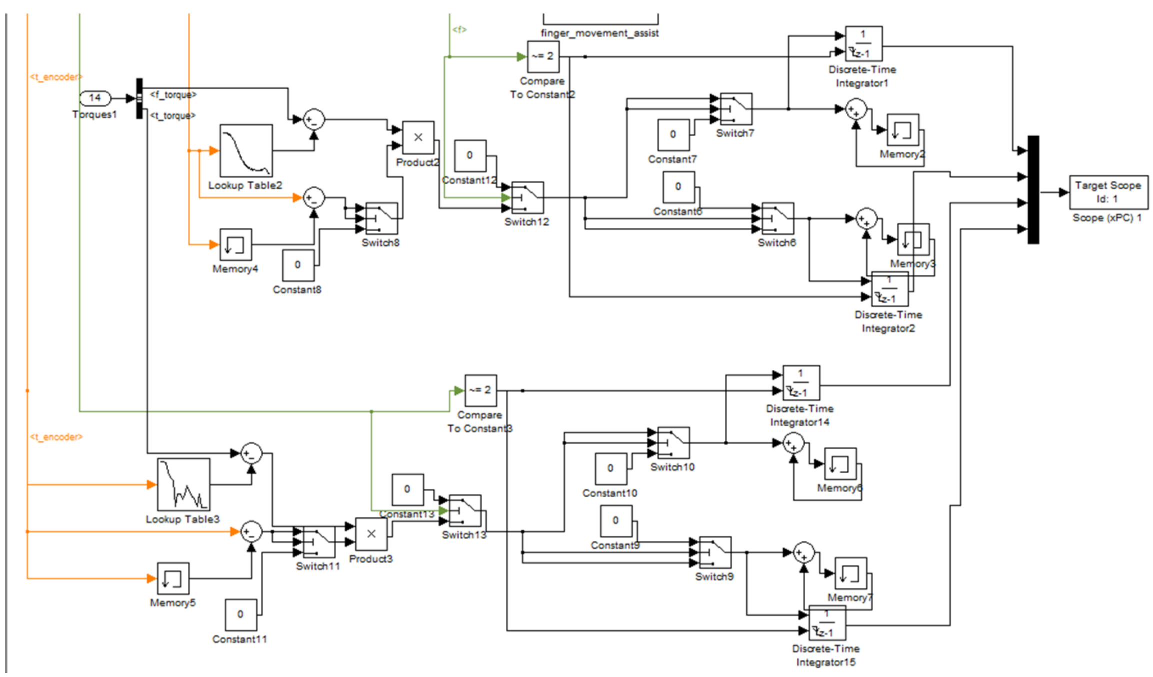

Fig. V.2: Screenshot of portion of model to calculate work in real-time

B. *Auto-Shaping Assistance Method*

The auto-shaping algorithm (Fig. V.3) is also housed in the "state decision" block. This algorithm was added to continuously challenge the user while responding to real-time changes in hypertonia. The subsystem is responsible for calculating the tone compensation provided at any given time and updates every three extension gates in the Gate Game. In the Stateflow block discussed above, the user's position at the end of each

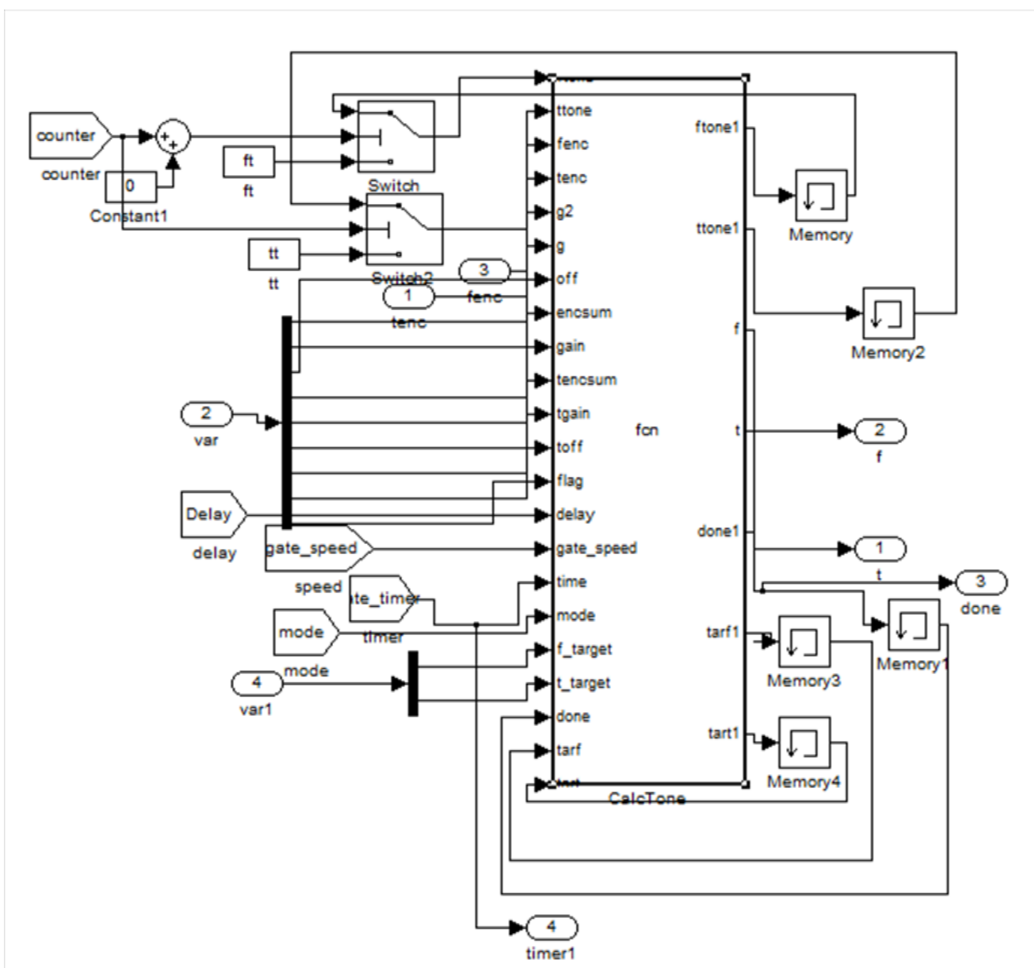

Fig. V.3: Screenshot of auto-shaping algorithm.

movement is compared to the gate to determine success or failure. The score is tallied and reset every three gates. If the user has succeeded at 2 or more gates, a signal is sent to decrease compensation. One success out of three prompts no change and zero successes results in a signal to increase compensation. The Stateflow block also calculates the average extension reached over each set of three gates and passes this value to the auto-adaptation algorithm.

The algorithm calculates the appropriate compensation based on these Stateflow inputs. To decrease compensation, the compensation is scaled down by 10 percent. In order to shape the assistance curve to better match the user's tone, the compensation is increased by an offset rather than scaling. The offset is introduced over a short ramp at the average maximum extension reached over the previous three gates. In this manner, assistance is provided where it is needed reducing the likelihood of maximal assistance reaching unsafe levels.

C. *Code*

The following code is the MatLab (Mathworks, Natick) script used to analyze the comparison study data in the assisted modes with delay. It is used to identify each extension phase and parse out the unassisted and assisted portions of each. The torque bias from the sensor is removed from the data before calculating work. Positive and negative work are then summated over the course of each half of the movement.

Displacement is recorded at the last sample point of each portion. Ultimately, the variables are concatenated into a master array for convenience.

```
%Program to calculate positive and negative work in HEXORR training
study
%Created 12/09/10
%Creates a matrix of pos and neg work that houses the work value for
each
%extension movement
close all
gate_speed=7; %total seconds per gate
freq=200; %sampling frequency
delay=round(freq*(gate_speed-gate_speed/7)/2); %point at which delay
ends and asst. starts
target_time=round(freq*(gate_speed/7));

%torque bias
thumb_bias = [0.504 0.504 0.504 0.504 0.503 0.4887 0.4815 0.4773 0.4406
0.4588 0.458 0.4501 0.4573 0.4703 0.4611 0.4542 0.4518 0.4398 0.4588
0.4389 0.4393 0.4393]; %added one to the beginning
finger_bias = [-0.0332 -0.0332 -0.0332 -0.0332 -0.0332 -0.0332 -0.0331
-0.0362 -0.0342 -0.039 -0.0509 -0.0448 -0.0459 -0.0534 -0.053 -0.0561 -
0.0665 -0.0693 -0.0743 -0.0882 -0.0915 -0.0954 -0.1057 -0.1178 -0.1251
-0.1441 -0.1544 -0.1675 -0.1688 -0.1789 -0.1936 -0.2025 -0.2083 -0.223
-0.2244 -0.2324 -0.2417 -0.2449 -0.2541 -0.2601 -0.2626 -0.2681 -0.2773
-0.2745 -0.2776 -0.2848 -0.28 -0.2837 -0.2936 -0.2905 -0.2873 -0.2955 -
0.2989 -0.2975 -0.2971 -0.2935 -0.2969 -0.3042 -0.302 -0.2986 -0.2995 -
0.3009 -0.2994 -0.2985 -0.305 -0.2992 -0.2974 -0.2984 -0.2939 -0.2905 -
0.2923 -0.2887 -0.2857 -0.2882 -0.2947 -0.2934 -0.3051 -0.3109 -0.3134
-0.3235 -0.3235 -0.3235]; %added one to the beginning


%establish variables from loaded data
f_torque = data (:,5);
t_torque = data (:,6);
f_state = data(:,9);
t_state = data(:,10);
time = data(:,11);

F_height=.85; T_height=.85; gate_width=15;
lF = ((80 * F_height)*0.5) + 37;
uF =lF+(gate_width-.1*gate_width-5);
lT = 37.5-((20*T_height)*2);
uT =lT +(gate_width-5);

lowerF=((lF-42.5)/.95)*2;
upperF=((uF-42.5)/.95)*2;
lowerT=((-lT+42.5)/2);
upperT=((-uT+42.5)/2);
```

```
% encF=((encoders.s_encoder/2)*.95)+42.5;
% encT=-(encoders.t_encoder*2)+42.5;
%Establish position variable and reset zero value, if necessary
if min(data(:,1)) < 0
    f_encoder = data(:,1) + abs(min(data(:,1)));
else
    f_encoder = data(:,1);
end

if min(data(:,2)) <0
    t_encoder = data(:,2) + abs(min(data(:,2)));
else
    t_encoder = data(:,2);
end

%initialize counting variables
t = 1; h = 1; e = 1; tt = 1; ht = 1; et = 1; i=2; j=1;
a=1; b=1; c=1; ta=1; ha=1; ea=1; aa=1; ba=1; ca=1;

f_possum=0; f_negsum=0; f_work=zeros(1,200000);
f_workpos=zeros(1,200000);
f_workneg=zeros(1,200000); f_possum_asst=0; f_negsum_asst=0;
% pos_w=zeros(1,8); neg_w=zeros(1,8); disp=zeros(1,8);
% pos_tor=zeros(1,8); neg_tor=zeros(1,8);
pos_w=zeros(1,30); neg_w=zeros(1,30); disp=zeros(1,30);
pos_tor=zeros(1,30); neg_tor=zeros(1,30);
pos_w_asst=zeros(1,30); neg_w_asst=zeros(1,30); disp_asst=zeros(1,30);
pos_tor_asst=zeros(1,30); neg_tor_asst=zeros(1,30);

t_possum=0; t_negsum=0; t_work=zeros(1,200000);
t_workpos=zeros(1,200000);
t_workneg=zeros(1,200000); t_possum_asst=0; t_negsum_asst=0;
% t_pos_w=zeros(1,8); t_neg_w=zeros(1,8); t_disp=zeros(1,8);
% t_pos_tor=zeros(1,8); t_neg_tor=zeros(1,8);
t_pos_w=zeros(1,30); t_neg_w=zeros(1,30); t_disp=zeros(1,30);
t_pos_tor=zeros(1,30); t_neg_tor=zeros(1,30);
t_pos_w_asst=zeros(1,30); t_neg_w_asst=zeros(1,30);
t_disp_asst=zeros(1,30);
t_pos_tor_asst=zeros(1,30); t_neg_tor_asst=zeros(1,30);
stop=0;

% plot(data(:,1)); hold all; plot(data(:,2));
%calculate positive and negative work
while i < length(f_encoder) && j<31
    i;
    j;
    start_asst=i+delay;
    while f_state(i)~=4 && t_state(i)~=4 && stop~=1 && i<start_asst
        %         i
        %         start_asst
        %             ((f_state(i)==4 & f_state(i)-f_state(i-1)>0) |
(t_state(i)==4
        %             & t_state(i)-t_state(i-1)>0))==0 && stop~=1
```

```
%          while i<start_asst
        f_encoderdiff = f_encoder(i) - f_encoder(i-1);
        f_bias = interp1(0:81,finger_bias,f_encoder(i),'linear');
        f_torquediff = f_torque(i) - f_bias;
        t_encoderdiff = t_encoder(i) - t_encoder(i-1);
        t_bias = interp1(0:21,thumb_bias,t_encoder(i),'linear');
        t_torquediff = t_torque(i) - t_bias;

        if f_encoderdiff > 0 && f_state(i) == 1  %changed >= to >
            f_work(t) = f_encoderdiff * f_torquediff;
            %disp(j)=disp(j)+f_encoderdiff;
            if f_work(t) > 0                 %changed >= to >
                f_workpos(h) = f_work(t);
                f_workpos(h);
                f_possum= f_possum + f_workpos(h);
                h = h+1;
            elseif f_work(t)<0                 %added elseif instead
of else
                f_workneg(e) = f_work(t);
                f_workneg(e);
                f_negsum = f_negsum + f_workneg(e);
                e = e+1;
            end
            if f_torquediff >pos_tor(j)
                pos_tor(j)=f_torquediff;
            elseif f_torquediff <neg_tor(j)
                neg_tor(j)=f_torquediff;
            end
            t = t + 1;
        end


        if t_encoderdiff > 0 && t_state(i) == 1  %changed >= to >
            t_work(a) = t_encoderdiff * t_torquediff;
            %disp(j)=disp(j)+f_encoderdiff;
            if t_work(a) > 0                 %changed >= to >
                t_workpos(b) = t_work(a);
                t_workpos(b);
                t_possum= t_possum + t_workpos(b);
                b = b+1;
            elseif t_work(a)<0                 %added elseif instead
of else
                t_workneg(c) = t_work(a);
                t_workneg(c);
                t_negsum = t_negsum + t_workneg(c);
                c = c+1;
            end
            if t_torquediff >t_pos_tor(j)
                t_pos_tor(j)=t_torquediff;
            elseif t_torquediff <t_neg_tor(j)
                t_neg_tor(j)=t_torquediff;
            end
            a = a + 1;
```

```
        end

        if i < length(f_encoder)
            i=i+1;
        else
            stop=1;
        end
        %          end
        disp(j)=f_encoder(i);
        t_disp(j)=t_encoder(i);
    end
    %          i
    %          start_asst+delay
    while f_state(i)~=4 && t_state(i)~=4 && stop~=1 &&
i<start_asst+delay

        %          if i>=start_asst%while i<start_asst+delay; %time when
the gate reaches the target
        f_encoderdiff = f_encoder(i) - f_encoder(i-1);
        f_bias = interp1(0:81,finger_bias,f_encoder(i),'linear');
        f_torquediff = f_torque(i) - f_bias;

        t_encoderdiff = t_encoder(i) - t_encoder(i-1);
        t_bias = interp1(0:21,thumb_bias,t_encoder(i),'linear');
        t_torquediff = t_torque(i) - t_bias;
        if f_encoderdiff > 0 && f_state(i) == 1  %changed >= to >
            f_work_asst(ta) = f_encoderdiff * f_torquediff;
            %disp(j)=disp(j)+f_encoderdiff;
            if f_work_asst(ta) > 0                    %changed >= to >
                f_workpos_asst(ha) = f_work_asst(ta);
                f_workpos_asst(ha);
                f_possum_asst= f_possum_asst + f_workpos_asst(ha);
                ha = ha+1;
            elseif f_work_asst(ta)<0                   %added elseif
instead of else
                f_workneg_asst(ea) = f_work_asst(ta);
                f_workneg_asst(ea);
                f_negsum_asst = f_negsum_asst + f_workneg_asst(ea);
                ea = ea+1;
            end
            if f_torquediff >pos_tor_asst(j)
                pos_tor_asst(j)=f_torquediff;
            elseif f_torquediff <neg_tor_asst(j)
                neg_tor_asst(j)=f_torquediff;
            end
            ta = ta + 1;
        end

        if t_encoderdiff > 0 && t_state(i) == 1  %changed >= to >
            t_work_asst(aa) = t_encoderdiff * t_torquediff;
            %disp(j)=disp(j)+f_encoderdiff;
            if t_work_asst(aa) > 0                    %changed >= to >
                t_workpos_asst(ba) = t_work_asst(aa);
```

```
                t_workpos_asst(ba);
                t_possum_asst= t_possum_asst + t_workpos_asst(ba);
                ba = ba+1;
            elseif t_work_asst(aa)<0                  %added elseif
instead of else
                t_workneg_asst(ca) = t_work_asst(aa);
                t_workneg_asst(ca);
                t_negsum_asst = t_negsum_asst + t_workneg_asst(ca);
                ca = ca+1;
            end
            if t_torquediff >t_pos_tor_asst(j)
                t_pos_tor_asst(j)=t_torquediff;
            elseif t_torquediff <t_neg_tor_asst(j)
                t_neg_tor_asst(j)=t_torquediff;
            end
            aa = aa + 1;
        end

        if i < length(f_encoder)
            i=i+1;
        else
            stop=1;
        end
        disp_asst(j)=f_encoder(i);
        t_disp_asst(j)=t_encoder(i);
        %          end
    end

    while f_state(i)~=4 && t_state(i)~=4 && stop~=1
        if i < length(f_encoder)
            i=i+1;
        else
            stop=1;
        end
    end
    done1=i
    %          if (f_state(i)==4 & f_state(i)-f_state(i-1)>0) |
(t_state(i)==4 & t_state(i)-t_state(i-1)>0)
    %                  disp(j)=f_encoder(i-200);
    %                  t_disp(j)=t_encoder(i-200);
    %          end

    pos_w(j)=f_possum;
    neg_w(j)=f_negsum;
    pos_w_asst(j)=f_possum_asst;
    neg_w_asst(j)=f_negsum_asst;
    while ((f_state(i)~=1) || (t_state(i)~=1)) && stop~=1 %f_encoder(i)
> 10
        if i < length(f_encoder)
            i=i+1;
        else
            stop=1;
        end
```

```
    end
    f_possum=0; f_negsum=0; f_possum_asst=0; f_negsum_asst=0;

    t_pos_w(j)=t_possum;
    t_neg_w(j)=t_negsum;
    t_pos_w_asst(j)=t_possum_asst;
    t_neg_w_asst(j)=t_negsum_asst;
    t_possum=0; t_negsum=0;  t_possum_asst=0; t_negsum_asst=0;

    i=i+1; j=j+1;
end

f_var=vertcat(pos_w, neg_w, pos_tor, neg_tor, disp);
t_var=vertcat(t_pos_w, t_neg_w, t_pos_tor, t_neg_tor, t_disp);

f_var_asst=vertcat(pos_w_asst, neg_w_asst, pos_tor_asst, neg_tor_asst,
disp_asst);
t_var_asst=vertcat(t_pos_w_asst, t_neg_w_asst, t_pos_tor_asst,
t_neg_tor_asst, t_disp_asst);
```

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