CORTICOSPINAL AND STRENGTH ADAPTATIONS FOLLOWING UNILATERAL WRIST EXTENSOR TRAINING AFTER STROKE

by

Noah Michael Huntington Ledwell

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Abstract

Unilateral strength training of the less affected (LA) limb has been shown to improve strength bilaterally. This improved strength is referred to as cross-education in the literature. This intervention has the potential to be beneficial for individuals who cannot train both sides of the body due to post-stroke hemiparesis. To date only one group has researched cross-education in the upper limb in stroke, with varied results. The main purpose of our work was to determine if strength training of the LA forearm would change patterns of cortical excitability bilaterally after stroke, and additionally affect changes in strength and function bilaterally.

Twenty-four participants with chronic (> 6 months) stroke-related hemiparesis engaged in three baseline sessions separated by 4-7 days. During these sessions individuals' forearm strength, motor function, and motor impairment were tested, along with a TMS based assessment of corticospinal excitability and intracortical circuits. On a fourth visit participants completed their first training session using the LA arm, then were given the same wrist extension strength-training device to take home. Participants completed three 25-minute training sessions, weekly; one in the laboratory and the remaining two at home. After 5 weeks of training, participants returned to the laboratory for post-intervention retention tests. Cross-education increased strength in the LA wrist extensors ($p = 0.026$) and the untrained, more-affected (MA) wrist extensors ($p = 0.05$) in participants with chronic stroke, at the 1-week retention test. Further, LA arm strength remained increased at 5-week retention test ($p = 0.023$) despite there being no further training. There were strength improvements in the majority of participants in both their trained (17 of 24) and untrained (12_of 24) wrist extensors. There was a decrease in corticospinal inhibition in

the LA hemisphere, and a release of interhemispheric inhibition (IHI) bilaterally. A significant increases in motor function and a decrease in motor impairment was seen, respectively.

Results indicate that cross-education could be a valuable tool for increasing strength in chronic stroke. Cross-education training of the LA upper limb may allow individuals who do not have adequate function in their MA limb prior to training engage in rehabilitative interventions post-training.

Preface

The present thesis contains one experiment that has been completed by the candidate Noah Michael Huntington Ledwell, under the supervision of Dr. Lara A. Boyd. Experimental design and conception, data acquisition and analysis, data interpretation, and documentation were primarily the work of the candidate.

This experiment was a collaboration with Dr. Paul Zehr and the Rehabilitation Neuroscience Laboratory at the University of Victoria.

This Experiment and all associated methods were approved by the University of British Columbia (UBC)'s Clinical Research Ethics Board (certificate # H15-00055) and protocol in Victoria was approved by the UVIC Human Research Ethics Committee (protocol # 07-480-04d).

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List of Abbreviations

1RM: One repetition maximum

6MWT: Six-minute walk test

AMT: Active motor threshold

BBS: Berg Balance Scale

CL-iSP: Contralesional ipsilateral silent period

CS: Conditioning stimulus

CSI: Conditioned stimulus intensity

CSP: Cortical silent period

ECR: *Extensor carpi radialis*

EMG: Electromyography

FM: Fugl-Meyer

GABA: γ-aminobutyric acid

$GABA_A$: GABA receptor subtype A

$GABA_B$: GABA receptor subtype B

ICF: Intracortical facilitation

IHI: Interhemispheric inhibition

IL-iSP: Ipsilesional ipsilateral silent period

ISI: Interstimulus interval

iSP: Ipsilateral silent period

LA: Less-affected

M1: Primary motor cortex

MA: More-affected

MEP: Motor evoked potential

MRI: Magnetic resonance imaging

MSO: Maximal stimulator output

MVIC: Maximal voluntary isometric contraction

PAR-Q: Physical Activity Readiness Questionnaire

PMC: Pre-motor cortex

RC: Recruitment curve

rmANOVA: Repeated-measures analysis of variance

RMT: Resting motor threshold

SD: Standard deviation

SE: Standard error

SICI: Short-interval intracortical inhibition

SMA: Supplementary motor area

T0: Baseline

T1: Post-intervention

T2: Retention

TCI: Transcallosal inhibition

TMS: Transcranial magnetic stimulation

TS: Test stimulus

TUG: Timed up and go

UBC: University of British Columbia

UE-FM: Upper extremity Fugl-Meyer

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To my supervisory committee members, Drs. Paul Zehr and Jayne Garland, your expertise, criticism, and feedback have helped a great amount during my thesis time. Thank you, Dr. Zehr, without your research my thesis would not exist! Hopefully our work can help inform and better the lives of clinical practitioners and individuals living post-stroke.

To family, thank you for being around to help support me throughout my studies, without all of you (mostly mom and dad) I would not be here at this stage of my life. To friends, you have all been great influences helping me along this path, and more importantly, being there to help me relieve stress when not in school!

Dedication

To Mom, Dad, Sebastian, Abigail, and Aurora

1 Introduction and Purpose

1.1 Introduction

In 2013 it was estimated that approximately 405,000 Canadians were directly affected by stroke.[6] Among stroke survivors up to 85% of these Canadians experience hemiparesis (weakness or loss of function on one side of the body).[7] Between 55 and 75% of these individuals also suffer from functional limitations, which negatively impact their activities of daily living and diminish their health-related quality of life for years following stroke.[8] Approximately 36% of these persons have significant disabilities 5 years post-infarct.[6] Recently, advances in stroke treatments stress early intervention, which is shown to drastically reduce the risk of mortality after stroke.[9] However, development of treatments intended for improving function post-stroke have failed to keep pace, especially in the chronic stage (> 6 months post-infarct), when individuals are mainly community-dwelling and are no longer hospitalized.

A major consequence of post-stroke hemiparesis is motor weakness and increased muscle tone in the more-affected (MA) upper extremity. Together these cause a characteristic wrist and hand posture, in which the MA wrist is flexed and the fingers are clenched.[10] Evidence-based techniques such as constraint-induced movement therapy benefit a small percentage of the stroke population (~25%),[11] yet interventions such as these rely on a dose of massed practice that cannot be easily delivered, is expensive, and is not well tolerated.[12] Such issues highlight a need for rehabilitation scientists to develop a novel, cost-effective, and tolerable intervention to restore strength and function to the MA upper extremity after stroke.

During the past several years, unilateral strength training of the less-affected (LA) side has been studied to examine its affects on rehabilitation post-stroke.[13,14] Training of one limb has been shown to have a beneficial effect on the contralateral, untrained homologous limb in healthy young research participants.[15,16] This transfer of strength is frequently referred to in the literature as "cross-education".[16–19] This cross-education effect usually averages about 50% of the strength gain seen in the trained side,[16,20,21] yet it's magnitude of change has been shown to vary greatly depending on a number of variables such as: training length and protocol, and task characteristics.[22] Farthing et al.[17] showed a much larger increase in the cross-education effect than previous studies, when considering the strength gain in the untrained limb relative to the trained limb of young healthy females, mean age (± SE) age of 21.0 ± 0.5 years. They found that during a 6-week strength training protocol of maximal isometric ulnar deviation (n = 23) there was a 45.4% increase in strength of the trained muscles versus a 47.1% increase in strength in the untrained muscles, as well as an enlarged region of activation in the contralateral sensorimotor cortex as shown by functional magnetic resonance imaging (fMRI). Possible reasoning behind this observation is that ulnar deviation is a novel strength training task, and therefore there was a lower baseline level of strength in both arms at the onset of the intervention. During cross-education, there is a lack of muscle hypertrophy,[23] and few adaptations at the level of the spinal cord as Lagerquist, Zehr, and Doherty (2006) showed increased changes in the Hoffman-reflex of the trained plantar flexors, yet no change in Hoffman-reflex of the untrained side after 5 weeks of training.[24] Hence the transfer of strength across the arms has been attributed to supra-spinal neural mechanisms.[17] Likewise, fMRI studies have shown a bilateral activation on the primary

motor cortex (M1), supplementary motor area (SMA), and the pre-motor cortex (PMC), associated with unilateral physical activity.[25,26] This increased activation in contralateral M1 may reflect increased descending input to agonists, decreased input to antagonists, or a mixture of these two.

Carroll et al.[16] performed a mini-review on 17 studies to elucidate possible mechanisms for the cross-education effect. Looking at muscular, neural, spinal cord, and cortical mechanisms, they stated that there are two mechanisms that could explain how the untrained contralateral limb increases its strength. They propose that: 1) unilateral strength training could cause a "spillover" of neural drive to the untrained side, inducing adaptations in the control system of the untrained limb; or 2) that this strength training could cause neuromuscular adaptations in the control system for the trained limb accessible to the untrained limb.

Thus, cross education interventions could potentially impact rehabilitation, especially in individuals who cannot recruit muscles, have significant weakness or loss of function due to neurologic impairment.[18] Unilateral strength training could be crucial in the field of post-stroke intervention where upper limb hemiparesis is a common issue. Research has attempted to modify activity in the hemiparetic limb through direct training,[11,27] with varied results. A more feasible, yet understudied area, includes interventions that access inter-limb neural circuits, by training of the LA limb.[28,29] Morris et al. performed a systematic review of literature examining resistance training after stroke and concluded that resistance training has positive outcomes and can reduce musculoskeletal impairment following stroke.[27] Yet, in cases of severe hemiparesis, this result may not be feasible due to extreme weakness in the MA limb.

To date, unilateral strength training has only been studied twice in stroke.[13,14] First, Urbin et al. performed a study with six individuals (> 4 months post-stroke) who engaged in 16 sessions of wrist extensor training of the LA side. The authors found that this training was able to increase force-generating capacity in the untrained paretic, (MA) muscle group.[14] However, their protocol consisted of an 80% one-repetition maximum (1RM) training load, yet maximal voluntary isometric contractions (MVICs) have been shown to elicit the greatest cross-education effect.[13,15,19,21] More recently, Dragert and Zehr studied the cross-education effect in individuals with chronic (> 6 months post-infarct) stroke after unilateral ankle dorsiflexion training. They enrolled 19 participants in a 6-week intervention (3 times weekly) of maximal isometric dorsiflexion of the LA limb. They observed a 31% increase in dorsiflexion torque of the untrained, MA side, versus a 34% increase in the trained, LA side. They concomitantly found a significant bilateral increase of muscle activation using electromyography (EMG). More importantly, four individuals, who could not produce significant force on their MA side before the intervention, were able to do so afterwards.[13] This highlights a need for a study of cross-education using MVICs in the upper-limb of individuals with stroke, due to its potential usefulness for Canadians affected by post-stroke hemiparesis.

To further explore the cortical changes that may be associated with cross education neurophysiological mapping with TMS can be used. TMS is a non-invasive brain stimulation technique used to measure human neurophysiology along the corticospinal tract.[30] During TMS a magnetic pulse is applied over a muscle representation in the primary motor cortex (M1), which transsynaptically activates corticospinal neurons and produces a motor evoked potential (MEP) in the target muscle, which can be measured

using EMG.[31] MEPs can be quantified and measured using differing single- and paired-pulse TMS techniques, each of which can examine distinct aspects of cortical excitability, and intracortical circuits.[32]

Altered brain connectivity and excitability has been shown during all phases post-stroke using multiple methods of TMS.[33] M1 excitability imbalances between both hemispheres occur after stroke, and a restoration of these balances is associated with functional recovery.[34–36] Increased inhibition has been characterized post-stroke by a prolonged CSP.[37] Two separate studies in acute stroke from Liepert and Shimizu showed motor cortex disinhibition (a reduction of short-interval intracortical inhibition (SICI)) in both hemispheres following stroke.[38,39] This reduction could decrease unwanted inhibition in certain cortical representations, which could produce the intended movement and be beneficial for motor rehabilitation.[40] The effects of stroke on intracortical dacilitation (ICF) are inconsistent across the literature. Some studies reported no change in ICF after stroke,[39,41] while others show increased contralesional ICF.[38,42] TMS studies of individuals with stroke also show altered connectivity between hemispheres with asymmetric transcallosal interactions. Several of these studies have shown less transcallosal inhibition (TCI) generated in the ipsilesional M1 than usual, while the contralesional M1 continually demonstrates normal or higher levels of inhibition.[43,44] This imbalance results in a net increase of inhibition acting upon ipsilesional M1, which depresses it's excitability. Increased inhibition from the contralesional M1 to the ipsilesional M1 has been hypothesized to contribute to stroke-related functional deficits.[33,43]

Research shows that intracortical and interhemispheric changes are related to

functional outcomes in individuals with stroke.[45–47] Honaga et al.[46] showed that decreased SICI levels correlated with paretic motor function in the finger, Harris-Love et al.[47] found that greater inhibition measured from the contralesional ipsilateral silent period (CL-iSP) to the ipsilesional ipsilateral silent period (IL-iSP) is associated with more severe impairment. Recent work by Hayward et al. (in review) found that a decrease in inhibition from the ipsilesional hemisphere to the contralesional hemisphere is related to better motor function.[46,48,49] Importantly, altered interhemispheric and intracortical inhibition have the potential to predict functional outcomes,[48,49] and as such could inform researchers and practitioners of an optimal brain state for functional rehabilitation.

There is a need for more research in the areas of strength training, stroke, and TMS. Several studies have used TMS to explore the changes in M1 excitability and intracortical circuits bilaterally following unilateral strength training.[50–54] Pearce and Kidgell (2012) found a significant increase and reduction in MEP recruitment curve (RC) amplitude, respectively, in both the trained and untrained leg, following 8 weeks of unilateral leg strength training (n = 18).[51] Perez and Cohen found significant increases in MEP RCs, and significant decreases in SICI following unilateral strength training of the dominant wrist flexors. Their work determined that the higher the contraction intensity, the greater the increase in MEP RC amplitude and decrease in SICI, with a 70% of maximum contraction intensity eliciting a much greater effect than 30% maximum.[55] Very little research has been performed regarding changes in ICF following unilateral strength training of either the upper or lower limb. One study found a decrease in SICI with no change in ICF, in the upper limb.[56] This subsequent release of inhibition following unilateral strength training could be crucial in individuals with chronic stroke,

as it could relate to an increase in motor function.[49,57] Only one study has looked at the MEP RC and CSP in stroke after unilateral strength training. In this work there were no discernible changes;[14] however a MVIC strength training protocol, which has been shown to elicit the greatest unilateral transfer of strength, was not used. To date there is no research exploring changes in transcallosal inhibition (TCI) associated with cross-education. As cross-education is believed to be related to communication between hemispheres in the brain,[16] TCI could play an important role in mediating this phenomenon.

These gaps in the literature (cross-education, stroke, and TMS) highlight the need for a trial intervention that is: 1) 4-6-weeks long,[18,19,58] 2) employs MVICs in the upper limb of individuals with chronic stroke, and 3) employs neurophysiological mapping to gage the effect of the intervention on cortical excitability.

1.2 Motivation, Aims, and Hypotheses

The primary motivation for the present thesis was to examine the effects of a 5-week maximal strength training intervention of the LA wrist extensors on bilateral changes in strength, motor function and impairment, as well as intracortical and interhemispheric excitability. This thesis was designed with the intention to build upon the findings from a previous strength training intervention of the LA ankle dorsiflexors after stroke, to help establish the effects of this type of intervention in the upper limb, its effects on corticospinal excitability and intracortical circuits, and to inform future research in individuals living with stroke. In the present thesis there were two major aims:

Aim 1: To determine whether 5 weeks high-intensity unilateral strength training

of the LA wrist extensor muscles will increase muscle strength bilaterally following stroke.

Hypothesis 1: We hypothesized that undergoing a 5-week high-intensity unilateral strength training intervention would increase strength bilaterally in individuals with chronic stroke. The increase in strength measured in newton-metre (Nm) MVIC was hypothesized to be similar in each upper limb, consistent with previous literature on cross-education in stroke in the lower limb.[13] This experiment is described in **Chapter 2.**

Aim 2: To explore the effects of 5 weeks high-intensity unilateral strength training of the LA wrist extensors on bilateral changes in corticospinal excitability.

Hypothesis 2: We hypothesized that unilateral strength training of the less-affected wrist would increase corticospinal excitability and intracortical facilitation in both hemispheres, as well as decrease intracortical inhibition and interhemispheric inhibition. This experiment is described in **Chapter 2.**

Aim 3: To determine the effects of 5 weeks high intensity unilateral strength training of the LA wrist extensors on upper extremity changes in motor function and impairment.

Hypothesis 3: We hypothesized that undergoing a 5-week high-intensity unilateral strength training intervention would improve motor function in both upper extremities and decrease motor impairment in these extremities. We hypothesized that all changes would be more relevant when running a statistical analysis on individuals who improved in strength on the LA (trained side).

1.3 Rationale

Bilateral gains in strength that result from unilateral strength training give promise to the use of this intervention in individuals with hemiparesis due to neurological injury,[18] especially after stroke. The changes in corticospinal excitability and intracortical circuits associated with this training in healthy individuals[52,55] could provide individuals with stroke an optimal environment for rehabilitation.[33] To date, however, the only evidence for the effects of the cross-education effect in individuals with stroke come from the lower limb;[13] data from the upper limb are inconclusive given the use of lower training intensities.[14] In order to inform clinical research studies, as well as to translate these findings into practice, it is necessary to determine if training of the LA wrist extensors will result in a bilateral wrist extensor strength gain and possible improvement of function after stroke. Likewise, it is necessary to determine if the changes indexed by TMS is this experiment reflect a more ideal environment for neurological rehabilitation. The present thesis contributes to the existing research literature by providing an analysis of the effects of a 5-week MVIC training intervention of the LA wrist extensors has on strength changes in the MA and LA wrist extensors, upper extremity motor impairment and function, and changes in corticospinal excitability and intracortical circuits.

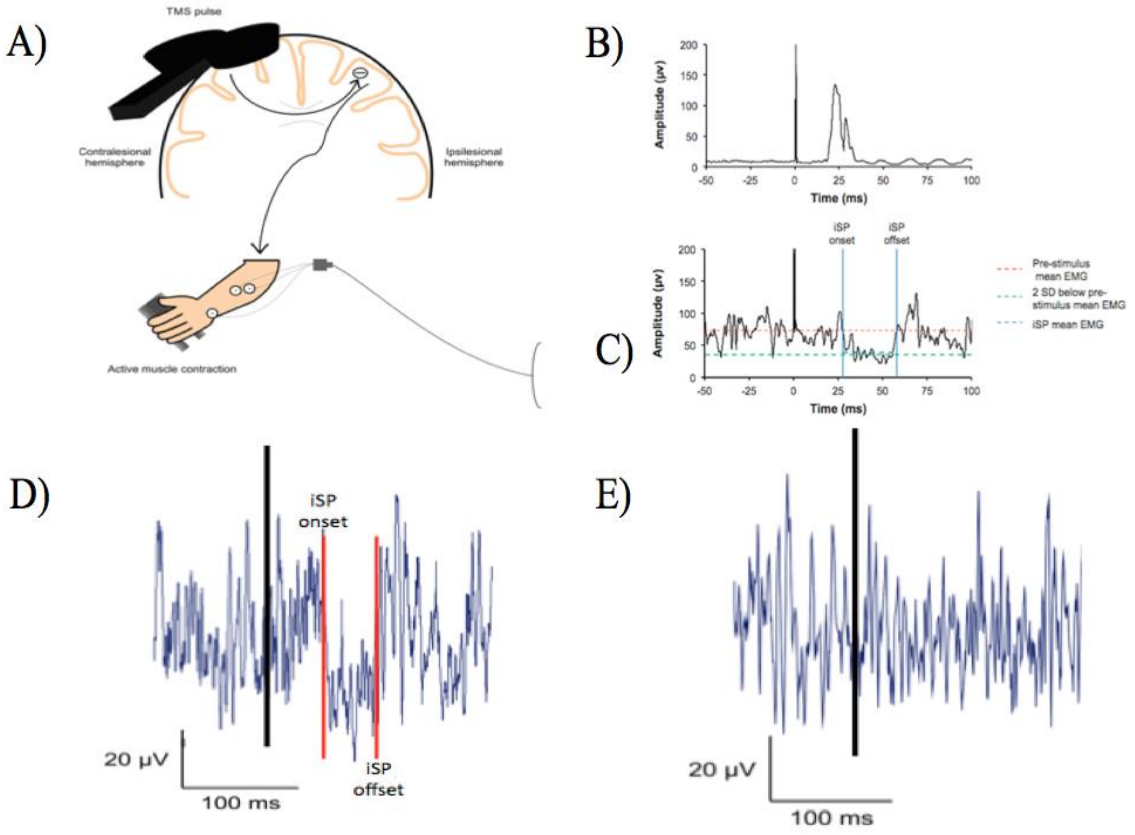

Figure 1-1. TMS evoked TCI. A) Diagram of TMS-evoked TCI, participants maintain a unilateral voluntary background muscle contraction in the arm ipsilateral to the TMS coil. A single TMS pulse is delivered over the motor cortex. The TMS pulse activates transcallosal pathways, which transmit an inhibitory signal to the active motor cortex. This elicits a transient quiescence in the background EMG in the active muscle. In the present example, TMS is delivered over the contralesional hemisphere to elicit the contralesional-iSP. TCI was also evoked with TMS delivered over the ipsilesional hemisphere to elicit the ipsilesional-iSP. **B) Rectified** motor evoked potential collected from the contralateral ECR muscle during the TCI procedure. **C)** Rectified EMG activity and iSP collected simultaneously from the ipsilateral ECR muscles. The iSP_{mean} ratio was calculated as: iSP mean EMG (blue line)/pre-stimulus mean EMG (red line). **D)** Output from an individual when TCI was present. **E)** Output from an individual when TCI was not present.[59]

1.4 Significance

Despite the existence of empirically supported upper extremity neurorehabilitation techniques (constraint-induced movement therapy[60] and task-specific training[61]), there is still a large number of stroke survivors who do not have a sufficient level of upper limb motor function to engage in these therapies.[14] The cross-educational effect of unilateral strength training could be a possible rehabilitation therapy for individuals with stroke,[62] given its recent success in increasing strength and improving function in the lower limb of individuals living with stroke.[13] Yet, the effects of maximal isometric strength training need to be researched in the upper extremity of individuals with hemiparesis after stroke before they can be applicable in a clinical setting. Therefore, we must fully elucidate the effects of upper extremity unilateral strength training of the LA wrist extensors over the course of a 5-week intervention in chronic stroke on strength, functional, and neurophysiological outcomes. If this intervention has beneficial results, it will be an important step in furthering rehabilitation therapies for individuals living with stroke in Canada. There will be greater rationale for larger clinical trials, with the eventual aim to incorporate this training into clinical application. Perhaps it will bridge the gap for stroke survivors of a certain functional level to move forward to other therapies, increasing their quality of life.

2 The Effect of Unilateral Strength Training of the Wrist Extensors on Corticospinal and Strength Adaptations After Stroke.

2.1 Introduction

In the present study we examined how 5 weeks of unilateral strength training of the LA wrist extensors would affect changes in strength, motor impairment and function, and select TMS outcomes. We targeted wrist extensors as a large proportion of stroke survivors suffer from hemiparetic loss in the upper extremity.[63] Given the implications for intracortical brain networks in contributing to the cross-education effect,[50–52,64] and the possible contribution of these changes to functional recovery post-stroke,[65–67] we also measured RC, CSP, SICI, ICF, and TCI. Wrist extensor torque, upper limb function and impairment, lower limb functional tests, and TMS measures were collected during three baseline tests separated by four days each, at a post-collection date after 5 weeks of unilateral (LA upper limb) strength training, and at a retention session after 5 weeks without training. We hypothesized that this training intervention would significantly increase wrist extension torque on both the trained (LA) and untrained (MA) sides, increase corticospinal excitability and ICF, reduce SICI, improve function as indexed by the Fugl-Meyer (FM), and decrease impairment as indexed by the Wolf Motor Function test (WMFT), relative to baseline values.

2.2 Materials and Methods

The present study was approved by UBC's Clinical Research Ethics Board (certificate # H15-00055). All participants independently provided written and verbal informed consent, in accordance with the principles of the Declaration of Helsinki.

2.2.1 Collaboration

The present study was a collaboration between the Brain Behaviour Laboratory at UBC, and the Rehabilitation Neuroscience Laboratory at the University of Victoria. Twelve participants were recruited at both sites (total n = 24). All 24 participants performed the strength testing and clinical measures at both sites. TMS measures were collected from the 12 participants undergoing the intervention at UBC, while the participants at the University of Victoria were tested for reciprocal inhibition and cutaneous reflexes.

2.2.2 Participants

Twenty-four individuals with chronic stroke (> 6 months post-infarct; mean age ± one standard deviation, SD: 67.8 ± 7.0 years; 3 females; **Table 2-1**) were recruited from Vancouver and Victoria, British Columbia and surrounding areas. This was a convenience sample based on a clinical population and previous stroke exercise intervention studies.[13,50,52] We included individuals who demonstrated unilateral limb weakness as a result of stroke. Hemiparetic upper limb weakness was assessed initially through verbal screening (e.g., "do you have trouble using your hand on your more-affected side?") and then confirmed in the laboratory by the upper extremity portion of the Fugl-Meyer assessment (UE-FM), performed by 3 licensed physiotherapists (SP at UBC, PL and KM at UVIC). Participants maintained current activity levels during the

study. Individuals were excluded if they were enrolled in an upper limb rehabilitation program or showed signs of dementia (score < 24 on the Montreal Cognitive Assessment). All participants were screened for contraindications to TMS **(**Assessed as per Rossi et al.; **Appendix E)**. No participant displayed any contraindications to TMS.

2.2.3 Experimental Design

The current study utilized a within-subjects repeated measures (pre-/post-test) design (see **Table 2-1)**. Participation consisted of 10 total laboratory visits, beginning with three baseline-measure test days[28] (B_{01}, B_{02}, B_{03}) in the weeks prior to intervention commencement. During the initial three sessions participants were provided with informed consent, and proceeded to participate in baseline clinical measures including: WMFT,[4]

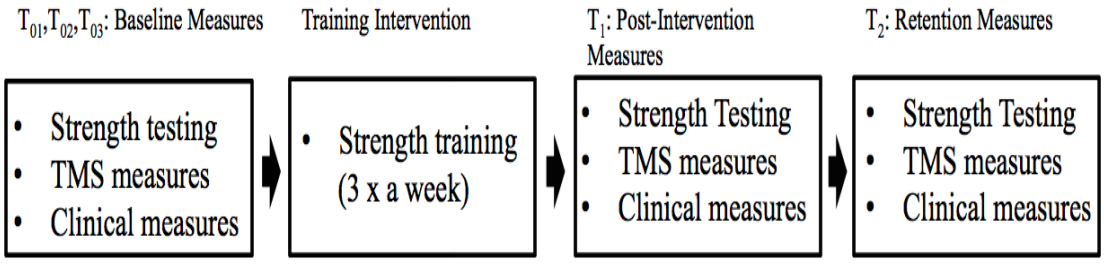

Figure 2-1. Experimental Procedure of the Study.

Table 2-1. Baseline participant characteristics.

Participant ID	Sex	MA Side	PSD (mo)	WMFT (MA Side)	WMFT (LA Side)	Modified WMFT (MA Side)	Modified WMFT (LA Side)	BBS	UE-FM	10 m Walk (s)	TUG (s)	6MWT (m)
CE01	F	L	68	23	78	1	48	51	39	15.2	15.3	227.2
CE02	F	R	34	18	78	5	56	27	11	na	na	na
CE03	M	L	110	7	83	0	51	40	9	11.9	17.4	206
CE04	F	R	181	15	43	0	43	42	28	13.1	14.5	223.7
CE05	M	L	185	10	58	2	42	37	20	12.4	14.6	265.0
CE06	M	L	100	38	57	22	35	35	48	12.1	15.6	252.3
CE07	M	L	137	99	104	52	65	54	60	3.7	5.5	555.7
CE08	M	R	137	66	123	45	82	42	54	6.8	13.2	350.3
CE09	M	R	302	3	76	0	55	35	5	10.2	15.1	271.3
CE10	M	R	64	51	60	30	42	53	54	6.9	11.4	304.0
CE11	M	R	125	5	70	0	49	50	5	na	na	na
CE12	M	R	195	3	74	0	51	41	11	na	na	na
P01	M	R	32	na	na	0	24	51	22	13.2	18.1	241.2
P02	F	L	96	na	na	0	28	48	5	12.2	19.4	278.4
P03	M	R	71	na	na	0	21	49	63	9.4	15.2	325.3
P04	M	L	90	na	na	17	25	46	2	8.6	14.2	287.4
P05	M	L	120	na	na	0	19	56	55	5.9	11.1	581.6
P06	M	R	94	na	na	8	25	46	37	14.3	17.3	213.5
P07	F	L	160	na	na	17	23	35	3	34.5	37.2	78.1
P08	M	L	231	na	na	0	25	55	22	7.1	11.7	465.0
P09	M	L	75	na	na	0	22	52	15	7.2	17.6	321.8
P10	F	R	249	na	na	0	29	41	10	12.1	24.0	255.8
P11	M	R	132	na	na	0	22	41	11	23.6	32.4	130.9
P12	M	L	93	na	na	8	22	31	40	44.0	50.6	67.6
Mean (SD)	**F = 6, M =18**	**L = 12, R = 12**	**128.4 (66.1)**	**28.1 (28.8)**	**75.2 (20.7)**	**8.7 (14.5)**	**37.7 (16.3)**	**44.1 (7.9)**	**26.2 (20.2)**	**13.6 (9.4)**	**18.6 (9.9)**	**281.1 (126.8)**

CE, participants at UBC; P, participants at UVIC; MA, more-affected; LA, less-affected; na, data not available; PSD, post-stroke duration; WMFT, Wolf Motor Function Test rate; BBS, Berg Balance Scale; UE-FM, upper extremity portion of the Fugl-Meyer Assessment; TUG, Timed Up and Go Test; 6MWT, Six-Minute Walk Test.

UE-FM,[68] Berg Balance Scale (BBS),[5] Timed Up and Go (TUG),[69] timed 10 m Walk, and the Six-Minute Walk Test (6MWT).[70] Participants underwent baseline TMS measures (see **2.2.6 Neurophysiology**), followed by baseline MVIC testing. Identical baseline testing occurred on three separate sessions, separated by four days each. Following baseline testing, participants performed a 5-week strength training intervention (see **2.2.4 Training protocol**). Baseline measures were repeated after the five-week intervention (T_1) and again after five weeks without intervention (T_2).

Both labs collected force measures across the three timepoints. FM was collected at both labs for T_0 and T_1, and for T_2 at the Brain Brehaviour Laboratory. All TMS measures were collected with the 12 participants at UBC. WMFT measures were collected across all timepoints at UBC, whereas an abbreviated WMFT was performed at UVIC. Lower limb clinical measures were collected at both labs for T_0 and T_1. UVIC collected other spinal outcome measures which will not be discussed in this thesis. The current thesis focuses on strength and clinical measures from 24 participants, and TMS measures from 12 participants.

2.2.4 Training Protocol

Volunteers visited the laboratory the same day weekly for 5 weeks. Participants were seated during training. Training duration was approximately 25 minutes per session and occurred once per week in the lab, with feedback given regarding training technique. Two additional sessions were completed weekly at home with the requirement that participants contacting the laboratory upon session completion. Participants were provided with a standardized audio recording, intended to mimic feedback provided in lab. The recording consisted of instructions to participants for all aspects of the training protocol (i.e., warm-up, procedure, when to contract, when to relax, as well as verbal encouragement). This ensured that instruction and timing was

consistent throughout participants and over time. Training was performed for use of a custom strength-training device (**Figure 2-2)** constructed at the University of Victoria. The device recorded training contraction data, which were stored offline on a memory card and used to track protocol compliance and measured a temporal profile of strength gains. Training commenced with a warm-up consisting of 3 sets of 5 submaximal repetitions on the LA training arm, followed by 5 sets of 5 wrist extensor MVICs. Contractions were held for 5 s with 2 s of rest between repetitions, and 2 min of rest between sets. These measures were chosen because they follow previously established strength training protocols,[71], as well as prior cross-education studies in healthy individuals[19] and in persons with stroke.[13] Participants were instructed during training to relax the MA arm, and were reminded by researchers if contractions were noticed.[13,20]

2.2.5 MVIC

Participants engaged in 12 total attempts (two orientations, neutral and prone; two directions per orientation, flexion and extension; and three contractions per direction) per arm. Contractions were held for 5 s and were separated by 2 min of rest. Force was measured with a 3D force transducer (ATI Industrial Automation Gamma DAQ F/T Transducer; **Figure 2-2)** and converted to a vector of wrist torque. Raw data from these trials was analyzed offline with custom written software on the MATLAB platform (Version R2013b, The Mathworks, Natick, MA, USA), and recorded as wrist torque in the X, Y, and Z directions as well as total wrist torque. Total wrist extension torque was calculated from the torque measured in the X,Y, and Z directions using the formula $\sqrt{(X^2 + Y^2 + Z^2)}$. This value of total wrist extension torque was used to index participants' changes in strength.

2.2.6 Neurophysiology

Single- and paired pulse TMS assessments were conducted during all baseline sessions, post training, and at retention. The order of TMS and MVIC was randomized. During all procedures participants were seated in a relaxed position with their hands rested on a pillow on their lap. All procedures were performed bilaterally. If it was not possible to elicit an ipsilesional MEP (5/12), the contralesional M1 hotspot was mirrored using a neuronavigation system (see **2.2.6.2 TMS**) to provide a target and only the TCI procedure was performed over the ipsilesional hemisphere, while all specified TMS protocols were performed over the contralesional hemisphere.

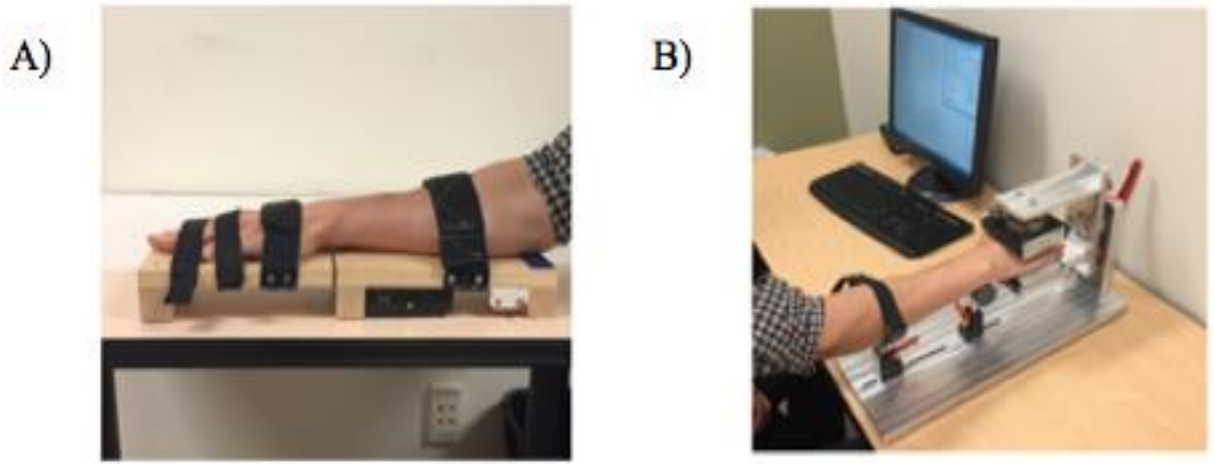

Figure 2-2. Custom strength training device and 3D force transducer. A) Custom strength training device, at zero; training sessions were completed with this device at lab and at home. **C)** 3D force transducer, participants baseline, post, and retention data were measured on this device. Distance between force transducer and base pad was measured and kept the same per participant.

2.2.6.1 EMG

For the TMS sessions, participants were fitted with bipolar electrode configurations (Kendall™ Ag^+/AgCl Foam Electrodes with Conductive Adhesive Hydrogel, Covidien™, Mansfield, MA, USA) over the bellies of both *extensor carpi radialis* (ECR) muscles. Ground electrodes were placed over the dorsal surface of each hand. EMG activity was sampled and monitored using a PowerLab 8/30 data acquisition system and BioAmp biological amplifier (AD Instruments Inc., Colorado Springs, CO, USA). Surface EMG was collected using LabChart software (LabChart 7.0, AD Instruments Inc., Colorado Springs, CO), and was pre-amplified at 1000x, band-pass filtered at 10-1000 Hz, and sampled at 2000 Hz. EMG collection was triggered by an external stimulus (TMS) and recorded in a 500 ms time window relative to the stimulus (100 ms pre-400 ms post-stimulus).

For MVIC sessions, participants were fitted with a bipolar electrode configuration on the bellies of both *flexor carpi radialis* (FCR) muscles. An extra ground electrode was placed over both lateral epicondyles. EMG collection was started upon the beginning of contraction and continuously collection for 10 s. Electrode placement was based on anatomical landmarks during the first session and measured for exact placement each visit.[72]

2.2.6.2 TMS

The TMS measures were only collected for half the sample, the 12 participants undergoing data collection at UBC. Monophasic TMS stimuli were delivered from two 200^2 Magstim magnetic stimulators connected by a $BiStim^2$ unit, via a 70 mm diameter P/N 9790 figure-of-eight coil (Magstim Co. Ltd., Whitland, Carmarthenshire, UK), at a frequency of 0.25 Hz. Coil location and trajectory for the ECR M1 representation were plotted and monitored using a Brainsight™ neuronavigation system and a standard anatomical image template (Rogue

Research Inc., Montreal, QC, Canada). Coil and participant localization in space were calibrated during each experimental session. For all procedures the TMS coil was held tangentially to the participant's skull, with the handle pointing laterally and posteriorly at 45^{o} to the mid-sagittal plane.[73] After plotting the ECR M1 representation, we determined the participants' resting motor threshold (RMT), defined as the lowest % maximum stimulator output (MSO) required to produce a 50 μV amplitude MEP peak-to-peak in the relaxed ECR, in at least 5/10 consecutive TMS stimuli. RMT was found for both the contralesional and ipsilesional hemisphere(when possible). RMT could only be found in 5 of 12 participants in the ipsilesional hemisphere. Following this, we determined the participants' active motor threshold (AMT), defined as the % MSO required to produce a 200 μV peak-to-peak amplitude MEP in an active ECR, in at least 5/10 consecutive TMS stimuli. Participants held an ECR contraction of 20% MVIC during these AMT stimuli. AMT could only be evoked in the ipsilesional hemisphere from 7 of 12 participants.

2.2.6.3 Single-pulse TMS

The most basic measure of cortical excitability is resting motor threshold (RMT) which is defined as the percentage of maximal stimulator output (% MSO) required to produce a 50 μV MEP on 5/10 trials with the participant at rest. Active motor threshold (AMT) is the percentage of MSO required to produce a 200 μV MEP on 5/10 trials while the participant holds a light contraction (10-20% MVIC) of the target muscle group.[59,74] MEP recruitment curves (RCs) use a range of stimulus intensities, based upon a resting motor threshold (RMT) or active motor threshold (AMT), to quantify the excitability of multiple populations of corticospinal neurons. The slope of the RC represents the ability of M1 excitability to be upregulated, which is

indicative of the strength of corticospinal connections.[59,75] EMG responses to TMS during sustained contractions also produce a cortical silent period (CSP), which is seen as a prolonged decrease in EMG activity following an MEP. CSPs are dependent on recovery at the level of M1, and are thought to be underpinned by both cortical and spinal mechanisms.[59] To characterize changes in corticospinal excitability, we plotted a simple linear regression line through the Stimulus Intensity (% AMT) versus Normalized MEP Amplitude (%AMT) recruitment curve, and calculated the slope of this relationship. This approach has been previously used to assess corticospinal excitability.[77–79] Additionally, since individuals were holding 20% MVIC during MEP RC collection, we extracted CSP values, based on the prolonged decrease in EMG activity following MEP elicitation. These were used as complementary information to MEP RC, for examining corticospinal excitability.

For TCI (see **Figure 1-1**), Single-pulse TMS can measure interhemispheric communication through the corpus callosum between M1 representations termed transcallosal inhibition (TCI). TMS was used to evoke a silent period in background EMG activity during a contraction of the hand ipsilateral to the stimulation site. This silent period in the EMG was defined as the ipsilesional silent period (iSP).[80] When referring to TCI elicited over the contralesional hemisphere this silent period will be referred to as CL-iSP, and over the ipsilesional hemisphere as IL-iSP. During these trials, participants squeezed a handgrip dynamometer (AD instruments, Colorado Springs, CO) to produce a target of 50% maximum grip force output in the hand ipsilateral to the TMS coil placement. This force signal was transmitted to a computer through a PowerLab data acquisition system (AD instruments, Colorado springs, CO) and collected with LabChart (LabChart 7.0, AD instruments, Colorado Springs, CO). LabChart provided a visual target so that participants could hold this 50%

contraction. During contraction 10 TMS stimulations at 150% RMT[80] were delivered over the M1 hotspot ipsilateral to the active contraction. If no MEP could be elicited from the ipsilesional hemisphere, stimulations were delivered at 100% MSO. Participants were offered a break from the contraction when fatigued. TCI measures analyzed were iSP-mean: referring to the mean decrease in muscle activity amplitude during the iSP, and iSP-max: referring to the minimum level of muscle activity amplitude during the iSP.[80]

2.2.6.4 Paired-pulse TMS

Paired-pulse TMS techniques are used to explore inhibitory and excitatory motor cortical networks. SICI occurs when a subthreshold conditioning stimulus (CS) and a suprathreshold test stimulus (TS) are separated by an interstimulus interval (ISI) of 1-6 ms. This results in a suppression of the MEP evoked by the TS. [81,83] ICF is a period of increased intracortical excitability shown in response to a CS and TS delivered at ISIs of 10-15 ms.[59] SICI is a protocol used to explore the influence of M1 inhibitory interneurons on the excitation of M1 pyramidal tract neurons.[59] ICF is a period of increased intracortical excitability resulting in test-stimulus (TS) MEP facilitation.[59,81] These two mechanisms are important in marking changes in intracortical excitability,[31,75] and assessing these circuits can provide important information pertaining to neuronal change in M1.[59] The conditioning-stimulus (CS) for SICI and ICF protocols was set at 80% AMT and the TS was set at the necessary stimulus intensity to consistently evoke an MEP of .3-.5 mV[82] in the ECRThis results in a suppression of the MEP evoked by the TS. [81,83] The ISI for SICI was set at 2 ms and for ICF at 12 ms, which have been shown to produce intracortical inhibition and facilitation, respectively.[31,81] In the ipsilesional hemisphere we could only elicit a TS in 4/12 participants. Ten TS, 10 SICI, and 10 ICF stimuli were delivered in a pseudo-randomized order (5 TS, 10 SICI, 10 ICF, 5 TS). All TMS data was

recorded in LabChart and analyzed offline with custom MATLAB scripts (Version R2013b, The Mathworks, Natick, MA, USA).

2.2.7 Clinical Measures

The same licensed physiotherapist (SP) performed assessments for participants at the UBC site across all time-points for the UE-FM[84] and the BBS.[5] The TUG,[69] the 10 m Walk, 6MWT,[70] and the WMFT[4] were all performed by a trained assessor (NL) at UBC. At the UVIC site abbreviated versions of the WMFT and UE-FM were performed. The abbreviated form of the WMFT[4,85] included item #9 (lift can), #11 (lift paper clips), and #16 (fold towel). These items were performed for a quick assessment of gross and fine upper limb motor function, as well as bilateral upper limb motor function. Abbreviated versions of WMFT have been performed in past studies.[85] For the FM test, only the upper extremity portion was collected as a 'modified' FM test (UE-FM) including the upper extremity (36), wrist (10), hand (14), and co-ordination/speed (6) resulting in a total score of 66.[3,85]

2.2.8 Statistical Analyses

The following statistical tests were performed to evaluate the effects of the intervention on all dependent variables. Main statistical tests were performed using repeated measures analyses of variance (rmANOVAs). *Post hoc* analyses were performed using the Tukey correction, in the event of a significant main effect or interaction. All statistical tests were performed using STATISTICA software (version 13 Academic, StatSoft, Tulsa, OK, USA). Statistical significance was set at $p \leq 0.05$.

For the following statistical tests: T_0 = baseline (pre-intervention), T_1 = post (post-intervention) and T_2 = retention (5 weeks post-intervention). Any instance in which the number of participants analyzed (n) differs from full sample ($n = 24$) will be specified. All statistical tests

from T_0 to T_1 for strength and clinical measures data were performed with the full sample (n = 24). Due to three participants not returning to complete the retention session, retention tests at T_2 were performed with n = 21. Thus, separate rmANOVAs were performed to compare time-points T_0-$T_1$and T_0-T_2. TMS measures were analyzed for participants from UBC only (n = 12), and the contralesional and ipsilesional hemispheres were analyzed separately. For TMS measures there was a full dataset for contralesional hemispheres (n = 12), yet only 4 to 7 participants exhibited ipsilesional measures (the exact number depended on how many participants responded to the different measures). TCI could be elicited in all participants (n = 12).

2.2.8.1 Multiple Baselines

For all variables with multiple baselines, one-way (Time) rmANOVAs were first performed over the three baseline time-points (B_{01}, B_{02}, B_{03}). When there was no significant main effect of Time (i.e., no significant difference between multiple baselines; $p > 0.05$), all baseline data were averaged as one time-point (T_0).

2.2.8.2 Strength Gains

To examine changes in wrist extension torque across time-points (T_0, T_1, T_2) and arms, one-way (Time) rmANOVAs were performed for LA and MA wrist extension torques separately across each time-point (n=24).

2.2.8.3 Single-Pulse TMS

To examine changes in corticospinal excitability across time-points (T_0, T_1, T_2) one-way rmANOVAs were performed on MEP RC slope and CSP values. As mentioned above, these analyses were run separately for contralesional (n = 12) and ipsilesional (n = 4) hemispheres.

To examine changes in TCI across time-points (T_0, T_1, T_2) and hemispheres (ipsilesional, contralesional), separate two-way (Time × Hemisphere) rmANOVAs were performed for IL-

iSP-mean, IL-iSP-max, CL-iSP-mean, and CL-iSP-max values. As previously mentioned, these analyses were performed on the entire subset of participants who received TMS (n = 12).

2.2.8.4 Paired-Pulse TMS

To examine changes in intracortical inhibition (SICI) and facilitation (ICF) across time-points (T_0, T_1, T_2) separate one-way (Time) rmANOVAs were run for each hemisphere (ipsilesional n = 4, contralesional n = 12), expressed relative to unconditioned TS MEPS, as percent inhibition (SICI) and percent facilitation (ICF).

2.2.8.5 Clinical Measures

To test for changes in clinical outcome measures (UE-FM, WMFT) separate one-way (Time) rmANOVAs were run using the respective data at each time-point (T_0, T_1, T_2).

2.2.8.6. Secondary Analyses

To determine the magnitude of the cross-education effect and variables related to it elicited by the training intervention, we performed a follow-up analysis on all outcome measures for individuals who gained strength in the LA arm. This was conducted to validate the cross-education effect in the present dataset, given that strength gains in the trained (i.e., LA) arm are required to confirm the emergence of cross-education.[23]

To choose responders we used the following protocol: a 95% confidence interval was determined for the three baseline testing days using $\alpha = 0.05$, the standard deviation of the trained arms torque (Nm) for all baseline contractions, and the amount of contractions (9). If the mean torque (Nm) of the contractions at post (T_1) fell above this confidence interval the participant was considered a responder.

2.3 Results

2.3.1 Primary Analyses

2.3.1.1 Baseline Measures.

Separate one-way rmANOVA's were run between baseline time-points of all outcome measures that were collected at separate locations: UBC and UVIC (strength, m-WMFT, FM). There was no main effect of Location for MA wrist extension torque ($F_{(1,10)} = 1.248$, $p = 0.289$), LA wrist extension torque ($F_{(1,11)} = 3.526$, $p = 0.087$), FM ($F_{(1,11)} = 0.262$, $p = 0.618$), or MA m-WMFT ($F_{(1,11)} = 2.81$, $p = 0.122$). The participants' data for these measures was collapsed into one group ($n = 24$) for further analysis.

A one-way rmANOVA was run between the 3 baseline sessions for each outcome measure. No significant effects of Time were shown for any baseline measures B_{01}, B_{02}, or B_{03}, throughout the study and these were collapsed into one time-point (T_0).

2.3.1.2 Aim 1 - Strength Gains

Between T_0 and T_1 the one-way rmANOVA indicated a significant main effect of Time ($F_{(1,23)} = 5.779$, $p = 0.026$), indicating that wrist extension torque increased by 36.8% in the trained, LA limb. Similarly, for the untrained, MA limb, a significant main effect of Time ($F_{(1,22)} = 4.2254$, $p = 0.051$) indicated an increase of 41.9% wrist extension torque ($n = 23$). No differences were shown in the amount of change between sides ($p = 0.792$).

For differences between all three time-points (T_0, T_1, T_2) the one-way rmANOVA indicated a significant main effect of Time ($F_{(2,36)} = 1.796$, $p = 0.023$) for the LA limb ($n = 21$). Post hoc analysis using Tukey's HSD found that the gain of strength was significant between T_0 and T_1 ($p = 0.044$), as well as between T_0 and T_2 ($p = 0.043$), with no significant difference between T_1 and T_2 ($p = 0.999$).

These results suggest that wrist extension torque in the trained, LA limb, was increased immediately after training, and that this increase persisted at retention. No significant main effect of Time ($F_{(2,36)}$ = 1.7962, p = 0.180) was shown for the MA limb (n = 19) when all three levels of Time (T_0, T_1, T_2) were taken into account.

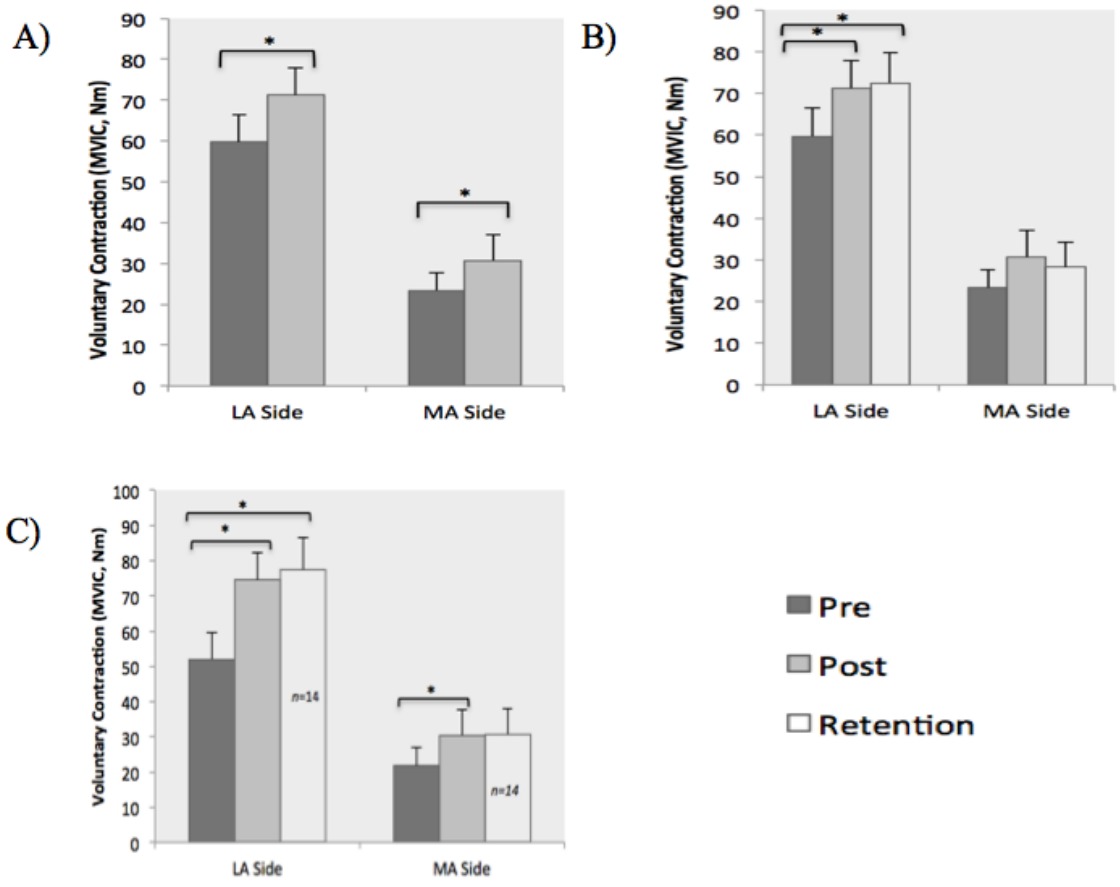

Figure 2-3. Unilateral wrist extensor training increased wrist torque bilaterally. Black bars represent group mean values of maximal voluntary isometric contraction (MVIC or wrist extension torque, in Newton-metres) pre-intervention (T_0), grey bars represent post-intervention (T_1), and white bars represent retention (T_2). **A)** Wrist extension MVIC significantly increased post-intervention on the LA (trained) side and the MA (untrained) side. **B)** Wrist extension MVIC significantly increased on the LA side (n = 21) following the intervention and this strength gain was retained at T_2. Strength gain was not significant on the MA side (n = 19). **C)**

Strength gains seen in responders, wrist extension MVIC significantly increased on the LA side and this strength gain was retained at T_2. Wrist extension MVIC increased significantly on MA side but was not retained at T_2 (n = 14). Data are mean ± SE, * denotes statistical significance ($p \leq 0.05$).

2.3.1.3 Aim 2 - Single-pulse TMS

See **Table 2-2** for all baseline (T_{01}-T_{03}) TMS measures. No significant effects were shown for RC in either hemisphere, indicating corticospinal excitability did not increase or decrease in either hemisphere after the intervention as indexed by this measure.

A lower CSP value (duration in ms) indicates a decrease in corticospinal inhibition. A significant main effect of Time ($F_{(1,11)}$, p = 0.018) showing a decrease in CSP duration was shown between T_0 and T_1, indicating there was a decrease in corticospinal inhibition to the ECR on the trained, contralesional side following the intervention (see **Figure 2-4**). At the CSI elicited for the ipsilesional hemisphere no CSP was visible and therefore no analysis could be performed.

Table 2-2. Baseline TMS measures.

Measure	Hemisphere	*n*	Time-point (Mean(SD))			
			Baseline 1 (T_{01})	**Baseline 2 (T_{02})**	**Baseline 3 (T_{03})**	***p*-value**
RMT (% MSO)	CL	12	53.7 (9.7)[a]	48.3 (12.5)[b]	50.0 (11.7)	0.009[*]
	IL	6	63.0 (10.3)	61.2 (16.7)	65.0 (15.0)	0.602
AMT (% MSO)	CL	12	46.7 (9.7)	43.7 (11.4)	45.4 (11.3)	0.480
	IL	7	66.1 (16.9)	63.0 (19.8)	64.6 (18.3)	0.834
SICI (% TS)	CL	12	93.0 (36.3)	80.0 (43.1)	88.4 (79.3)	0.761
	IL	4	66.1 (13.8)	na	na	na
ICF (% TS)	CL	12	151.8 (35.9)	129.6 (39.4)	123.8 (71.9)	0.371
	IL	4	135.9 (20.8)	na	na	na
CSP (s)	CL	12	0.13 (0.04)	0.12 (0.03)	0.14 (0.03)	0.299
	IL	na	na	na	na	na
RC Slope	CL	12	0.016 (0.013)	0.016 (0.010)	0.016 (0.007)	0.983
	IL	7	0.005 (0.004)	na	na	na
iSP-Mean (% ps mean EMG)	CL	12	80.9 (7.5)	78.7 (9.1)	82.8 (6.4)	0.472
	IL	12	77.1 (10.7)	76.1 (13.2)	72.7 (8.4)	0.533
iSP-Max (% ps min EMG)	CL	12	60.4 (15.2)	50.6 (12.4)	61.6 (16.4)	0.131
	IL	12	52.3 (18.1)	49.9 (20.2)	45.9 (11.9)	0.592

RMT, resting motor threshold; AMT, active motor threshold; % MSO, percentage of maximum stimulator output, transcranial magnetic stimulation; SICI, short-interval intracortical inhibition; ICF, intracortical inhibition; % TS, percentage of unconditioned test stimulus motor evoked potential; CSP, cortical silent period; RC, recruitment curve; iSP-Mean, mean ipsilateral silent period; % ps mean EMG; percentage of mean pre-stimulus peak-to-peak electromyography signal; iSP-Max, maximal ipsilateral silent period; % ps min EMG; percentage of minimum pre-stimulus peak-to-peak electromyography signal; CL, contralesional; IL, ipsilesional; na, data not available. [*], Statistically significant, $p \leq 0.05$; [a], significantly different from T_{02}; [b], significantly different from T_{01}.

Between T_0, T_1, and T_2 for CSP of the contralesional hemisphere (n = 9) there was no significant effect of Time ($F_{(2,16)}$ = 1.770, p = 0.202).

A higher value of pre-stimulus EMG/iSP mean indicates a decrease in inhibition. Between T_0 and T_1 there was neither a significant main effect of Hemisphere ($F_{(1,11)}$ = 1.768, p = 0.211), nor a significant Hemisphere × Time interaction effect ($F_{(1,11)}$ = 0.084, p = 0.778). However, we found a significant main effect of Time ($F_{(1,11)}$ = 6.939, p = 0.023), indicating that there was a decrease in inhibition shown in both hemispheres after the intervention (see **Figure 2-5**).

When taking into accout all time points (including retention), there was neither a significant effect of Hemisphere ($F_{(1,8)}$ = 1.658, p = 0.234), Time ($F_{(2,16)}$ = 1.957, p = 0.174), nor a significant Hemisphere x Time interaction ($F_{(2,16)}$ = 0.465, p = 0.637).

2.3.1.4 Paired-pulse TMS

SICI and ICF could only be elicited from the ipsilesional hemisphere of four participants during a single baseline session. As such, these measures were used for the T_0 time-point.

Increasing SICI values at T_0 relative to T_1 indicates a reduction of inhibition. There was no significant main effect of Time ($F_{(1,11)}$ = 0.167, p = 0.691), suggesting there was no significant change in intracortical inhibition in the contralesional hemisphere after the course of the intervention.

Increasing ICF values at T_0 relative to T_1 indicates an increase in intracortical facilitation. There was no significant main effect of Time in the contralesional hemisphere ($F_{(1,11)}$ = 0.68, p = 0.43), indicating no effect of the intervention on intracortical facilitation.

As mentioned above, we were only able to elicit paired-pulse responses in four participants on the ipsilesional side. A paired *t*-test showed no change between SICI at T0 (mean ± SD = 0.661 ± 0.138) and SICI at T1 (mean ± SD = 0.544 ± 0.144) ($p = 0.161$). A separate *t*-test showed no change between ICF at T_0 (mean ± SD = 1.359 ± 0.208) and T_1 (mean ± SD = 1.383 ± 0.462) ($p = 0.927$).

2.3.1.5 Aim 3 - Clinical Measures

See Table **2-2** for all pre-post clinical measures. Between T_0 and T_1 for the FM test there was a significant main effect of Time ($F_{(1,23)} = 15.682$, $p = 0.0006$) suggesting that upper extremity impairment was decreased after performing the intervention. FM data for T_2 was only collected at UBC. Furthermore, due to participant attrition the final number of participants who completed this measure at T_2 was smaller than those who performed the testing at T_0 and T_1 ($n = 9$). Between T_0, T_1, and T_2 there was a significant main effect of Time ($F_{(2,16)} = 26.763$, $p = 0.00001$) showing that decreased upper extremity motor impairment was still evident at retention in the sub-set of our sample. *Post hoc* testing indicated that there were significant differences between T_0 and T_1 ($p = 0.0003$), as well as between T_0 and T_2 ($p = 0.0002$). There was no significant difference between T_1 and T_2 ($p = 0.242$). These results indicate that participants who completed the entire experiment lessened their motor impairment after completing the intervention, and this improvement was sustained at retention testing.

Between T_0 and T_1 for the abbreviated WMFT of the LA (trained) arm there was a significant main effect of Time ($F_{(1,23)} = 5.204$, $p = 0.032$), showing an increase in upper limb motor function post-intervention. For the MA (untrained) arm there was a trend towards significance ($F_{(1,23)} = 3.936$, $p = 0.0593$), indicating that motor function of this arm tended to improve from T_0 to T_1. The full WMFT was performed at UBC ($n = 12$). Between T_0 and T_1 for

the full WMFT of the LA (trained) arm there was a trend toward significance ($F_{(1,11)} = 4.587$, $p = 0.055$). For the MA (untrained) arm there was a significant main effect of Time ($F_{(1,11)} = 13.199$, $p = 0.0039$), showing an increase in upper limb motor function post intervention. Between T_0, T_1, and T_2 there was no significant main effect of Time ($F_{(2,16)} = 2.872$, $p = 0.08$) for the LA arm ($n = 9$). There was a significant main effect of Time ($F_{(2,16)} = 4.47$, $p = 0.028$) for the MA arm ($n = 9$). *Post hoc* testing indicated there was a significant difference between T_0 and T_1 ($p = 0.022$), with no significant differences between T_1 and T_2 ($p = 0.29$) and T_0 and T_2 ($p = 0.34$).

2.3.2 Secondary Analyses

Following the statistical analyses of all participants, we regrouped the participants and performed the same statistical measures on only the participants who showed an improvement of strength in the LA (trained) arm. This analyses was to discern the effects of cross-education given that strength gains in the trained (i.e., LA) arm are required to confirm the emergence of cross-education.[23]

2.3.2.1 Strength Gains

For the 16 participants who showed improvement in the trained arm there was a significant main effect of Time ($F_{(1,15)} = 46.2$, $p = 0.00001$) for wrist extension torque between T_0 and T_1 in the LA (trained) arm, and a significant improvement in wrist extension torque in the MA (untrained) arm ($F_{(1,15)} = 5.3944$, $p = 0.0347$). Due to dropout only 14 participants completed T_2. For the LA arm there was a significant improvement in wrist extension torque between T_0, T_1, and T_2 ($F_{(2,26)} = 14.41$, $p = 0.00006$). *Post hoc* testing showed an improvement between T_0 and T_1 ($p = 0.00002$) and T_0 and T_2 ($p = 0.0005$) with no difference between T_1 and T_2 ($p = 0.918$) indicating that participants gained strength in the trained arm post-intervention,

and did not lose this increased strength at the retention time-point 5 weeks later. There was no main effect of Time for the MA arm ($F_{(2,26)} = 2.823$, $p = 0.078$); although, there was a trend towards significance.

Table 2-3. Strength and TMS measures.

Measure	**Condition**	***n***	**Time-point (Mean(SD))**			
			Pre (T0)	**Post (T1)**	***p*-value**	**Cohen's D**
LA Strength	n	24	59.72 (33.28)	71.25 (32.46)	0.023*	0.35
	R	16	52.07 (30.55)	74.58 (30.28)	0.000*	0.74
MA Strength	n	23	23.39 (20.79)	30.75 (31.2)	0.051	0.28
	R	16	21.78 (20.71)	30.49 (29.26)	0.034*	0.34
CSP	n	12	0.13 (0.03)	0.11 (0.03)	0.018*	0.45
	R	9	0.13 (0.03)	0.11 (0.04)	0.033*	0.46
TCI Mean	n	12	0.78 (0.08)	0.82 (0.06)	0.023*	0.5
	R	9	0.78 (0.06)	0.82 (0.09)	0.041*	0.47

n, full sample; R, responder; LA strength, force on the trained arm; MA strength, force on the untrained arm; CSP, cortical silent period; TCI mean, transcallosal inhibition mean.
*, statistically significant $p \leq 0.05$.

2.3.2.2 Single-Pulse TMS

No significant change was found for the LA (trained arm), contralesional recruitment curve slope or for the MA (untrained arm), ipsilesional recruitment curve slope.

For CSP duration between T_0 and T_1, there was a significant main effect of Time ($F_{(1,9)} = 6.28$, $p = 0.0335$) showing a decrease in CSP duration from the contralesional hemisphere ($n = 10$). This indicates there was a decrease in corticospinal inhibition to the ECR on the trained side following the intervention for individuals who gained strength in the trained (LA) upper limb (see **Figure 2-4**). We could not reliably identify any CSP in the ipsilesional hemisphere.

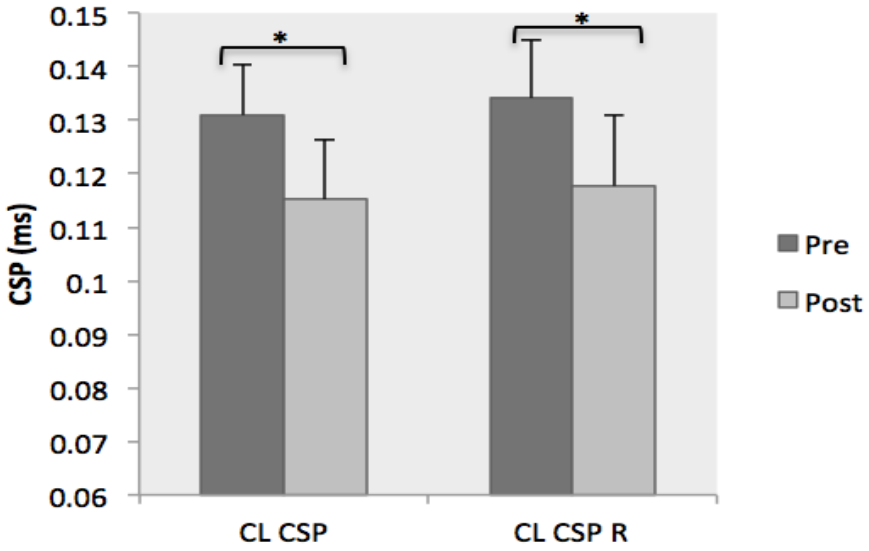

Figure 2-4. Corticospinal silent period from the trained wrist extensors elicited from the contralesional M1.

Black bars represent group mean values of the contralesional corticospinal silent period duration (CL-CSP, ms) pre-intervention (T_0), grey bars represent post-intervention (T_1). Bars on the left side are the means of the entire sample (n = 12), right side represents means of cross-education responders (CL SCP R, n = 10). In both cases CSP decreased significantly post-intervention. Data are mean ± SE. * denotes statistically significant ($p \leq 0.05$).

For iSP-mean between T_0 and T_1 for iSP-mean there was neither a significant main effect of Hemisphere ($F_{(1,9)} = 1.575$, $p = 0.211$), nor a significant Hemisphere × Time interaction effect ($F_{(1,9)} = 0.935$, $p = 0.778$). However, we found a significant main effect of Time ($F_{(1,9)} = 6.716$, $p = 0.041$), indicating that there was a decrease in inhibition shown in both hemispheres after the intervention (see **Figure 2-5**).

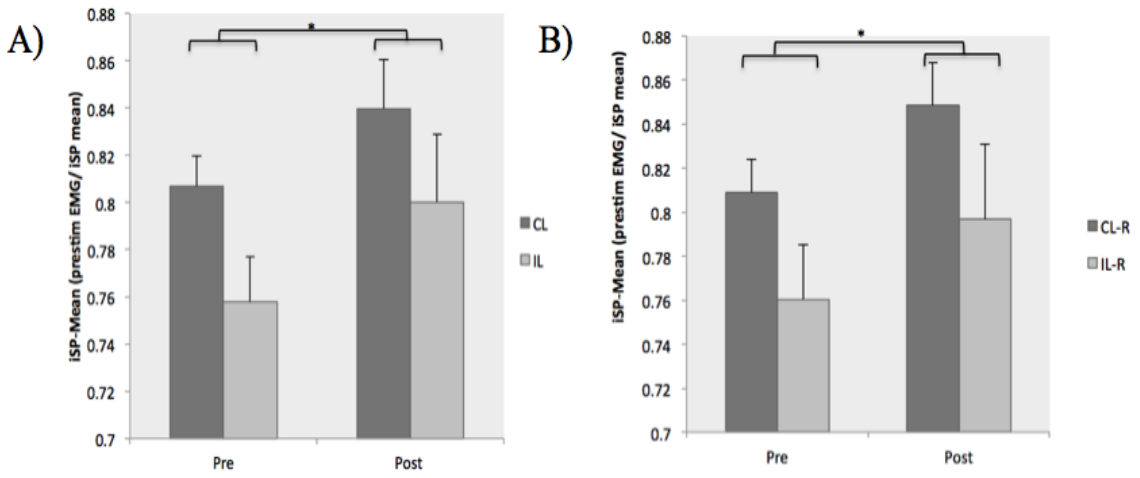

Figure 2-5. Transcallosal inhibition from both hemispheres.

Black bars represent group mean values for pre-stimulus EMG/ ipsilateral silent period mean pre-intervention (T_0), grey bars represent post-intervention (T_1). Bars on the left side are the means of the entire sample (n = 12), the right side represents means of cross-education responders (n = 10). A higher bar represents less inhibition. In both cases the iSP-mean significantly decreased post-intervention. Data are mean ± SE. *denotes statistically significant ($p \leq 0.05$).

2.3.2.3 Paired-pulse TMS

No changes were seen in SICI or ICF.

2.3.2.4 Clinical Measures

There was a significant main effect of Time ($F_{(1,15)}$ = 19.596, p = 0.0005) between T_0 and T_1 for Fugl-Meyer scores suggesting that upper extremity impairment was decreased after performing the intervention. Between T_0, T_1, and T_2 (n = 8), there was a significant main effect of Time ($F_{(2,14)}$ = 22.72, p = 0.00004). *Post hoc* testing indicated there were significant differences between T_0 and T_1 (p = 0.00006), T_0 and T_2 (p = 0.0002), with no significant

difference between T_1 and T_2 ($p = 0.346$), suggesting that upper extremity impairment was decreased after the intervention and stayed decreased at retention.

For the abbreviated WMFT of the LA (trained) arm between T_0 and T_1 ($n = 16$), there was a significant effect of Time ($F_{(1,15)} = 13.86$, $p = 0.002$), as well as for the MA (untrained) arm ($F_{(1,15)} = 6.46$, $p = 0.023$), suggesting that upper extremity motor function improved after the intervention for individuals who gained strength in the trained (LA) upper limb.

For the full WMFT ($n = 10$) there was a significant main effect of Time ($F_{(1,9)} = 8.94$, $p = 0.015$) between T_0 and T_1 for the LA arm and for the MA arm ($F_{(1,9)} = 9.61$, $p = 0.013$). Between T_0, T_1, and T_2, there was a significant main effect of Time ($F_{(2,14)} = 7.32$, $p = 0.007$) for the LA arm. *Post hoc* testing indicated there was a significant change between T_0 and T_1 ($p = 0.006$), with no significant difference between T_0 and T_2 ($p = 0.064$) or T_1 and T_2 ($p = 0.427$). This suggests that motor function improved in the trained arm after the intervention but did not stay significantly improved at retention for individuals who gained strength in the trained (LA) upper limb. Between T_0, T_1, and T_2 for the MA arm there was a significant main effect of Time ($F_{(2,14)} = 4.46$, $p = 0.031$). *Post hoc* testing indicated there was a significant change between T_0 and T_1 ($p = 0.026$), with no significant change between T_0 and T_1 ($p = 0.197$), or T_1 and T_2 ($p = 0.509$). This suggests that motor function improved in the untrained arm after the intervention but did not stay significantly increased at retention for individuals who gained strength in the trained (LA) upper limb.

Measure	Condition	*n*	Time-point (Mean(SD))			
			Pre (T0)	Post (T1)	*p*-value	Cohen's D
FM	n	24	26.2 (20.1)	28.7 (19.9)	0.000*	0.13
	R	16	26.7 (19.0)	29.9 (19.2)	0.000*	0.17
WMFT rate (LA)	n	12	75.2 (20.7)	85.9 (21.9)	0.055	0.48
	R	10	70.2 (16.1)	84.8 (18.0	0.015*	0.85
WMFT rate (MA)	n	12	28.1 (28.8)	34.7 (31.7)	0.004*	0.13
	R	10	25.4 (28.9)	31.9 (31.6)	0.012*	0.21
abbr-WMFT (LA)	n	24	37.7 (16.3)	42.5 (18.4)	0.032*	0.27
	R	16	39.2 (13.2)	47.3 (17.7)	0.002*	0.51
abbr-WMFT (MA)	n	24	8.7 (14.5)	10.6 (16.5)	0.059	0.13
	R	16	8.3 (14.5)	11.1 (18.0)	0.022*	0.17
BBS	n	24	44.1 (7.9)	45.5(7.5)	0.145	na
	R	16	45.1 (7.5)	46.0 (7.7)	0.503	na
TUG	n	21	18.6 (9.9)	18.4 (12.5)	0.806	na
	R	14	16.3 (7.1)	15.4 (7.0)	0.162	na
6MWT	n	21	281.8 (126.8)	299.7 (143.1)	0.425	na
	R	15	299.4 (131.9)	320.9 (150.4)	0.024*	na
10m Walk	n	21	13.5 (9.4)	12.7 (8.8)	0.008*	na
	R	14	12.3 (6.9)	11.5 (6.3)	0.073	na

Table 2-4. Clinical test measures.
n, full sample; R, responder; FM, fugl-meyer; WMFT, wolf motor function test; abbr-WMFT, abbreviated wolf motor function test; BBS, berg balance scale; TUG, timed up and go; 6MWT, six
minute walk test; 10m; 10 metre walk test; LA, less-affected side; MA, more-affected side;
*, statistically significant $p \leq 0.05$.

2.4 Discussion

The aim of the current study was to examine the effects of a 5-week MVIC strength training intervention of the LA wrist extensor muscles on bilateral gains in strength ("cross-education"), changes in corticospinal and intracortical excitability as indexed by TMS, and changes in clinical assessments. First, this experiment showed that individuals living with chronic stroke can significantly improve the strength and function of the paretic (MA) upper limb, by training the non-paretic (LA) upper limb. Second, we noted changes in corticospinal excitability and interhemispheric inhibition associated with a cross-education training program. Overall, this research shows that cross-education of the upper limb can be successful in individuals with chronic stroke when a maximal intensity unilateral strength training program is employed.

Aim 1: Strength Changes

The strength increases we observed in the trained (37%) and untrained (43%) upper limb were larger then those noted in previous cross-education studies in individuals with[13,14] and without stroke.[16,23] This magnitude of strength increase shown in the present study may be due to the fact that individuals with stroke generally had less baseline strength in both limbs compared to controls of a similar age.[86,87] Novel strength training tasks have been shown to elicit a greater strength gain in the untrained limb,[17,88] as was shown in this study. Large variability is observed in strength training in healthy individuals, with some showing no strength gains following training.[89] This indicates that cross-educational strength training in individuals with stroke can have robust effects, as our results were significant with eight non-responders. Cross-education occurs when the untrained limb gains a percentage of strength observed in the trained limb. Analyses

performed on individuals who were considered responders (increased in strength in the trained arm) showed more promising results of 63% and 53% in the trained, LA and untrained, MA arms, respectively. The strength gain in the untrained arm was not quite significant with the full sample ($p = 0.051$), it was significant within the cross-education responders ($p = 0.034$), showing that individuals who showed improvements in the LA (trained side, responders), improved strength in their MA (untrained) side.

As our sample was predominantly individuals with severe stroke (average FM score = 26.2),[90] these data indicate that a cross-education program may have the potential to be clinically useful during upper limb rehabilitation. This may be particularly true for individuals who are unable to engage in more task-specific upper-limb rehabilitation programs because of their poor motor function.[12,91] Given that this study consisted of individuals with chronic (> 6 months post-stroke) stroke (average 128.4 months), our data also highlight that the potential for upper limb rehabilitation long after stroke occurrence. It has been considered that best practice post stroke includes a program of motor-rehabilitation that contains a high amount of repetitions and long training period.[87] Comparatively, a key benefit of cross education is its short training time, (125 s per session, 3 × per week, for 5 weeks). Moreover, with two out of three sessions occurring in the participants' homes, our cross education intervention presents people with post-stroke hemiparesis a convenient, affordable motor rehabilitation paradigm.

Limb Dominance

In the literature, cross-education has been shown to be much stronger when individuals were training with their dominant arm and were right handed.[15] Farthing et al. (2005) show that the cross-education effect is only seen from right limb to left limb.[58]

Interestingly in our study, training with the dominant limb did not appear to have an effect in stroke. A paired t-test was ran with the change scores in Nm of the untrained arm between participants who trained with their dominant limb (mean ± SD = 6.08 ± 21.06; n = 11) and individuals who trained with their non-dominant limb (mean ± SD = 8.5 ± 11.44; n = 13). No difference was seen between the changes in strength gain (p = 0.371). In the case of chronic stroke, it could be that when an individual is forced to use their non-dominant side for everyday tasks due to hemiparetic damage, this side takes on characteristics of the dominant side.

Aim 2: Electrophysiology Changes

The reduction in the cortical silent period of the trained arm post-training observed in our study agrees with previous literature in cross-education in individuals without stroke.[92,93] For example, Kidgell et al.[92] showed that four weeks MVIC training of the dominant wrist flexors decreased the CSP duration significantly in both arms following training in a group of healthy control participants. Our research is the first to show this decrease in CSP duration in the trained, LA hemisphere following unilateral strength training in individuals with chronic stroke, indicating that this CSP decrease may contribute to the strength gains observed on the trained, MA upper limb. We were not able to elicit a CSP on the ipsilesional (untrained) side for the four participants with ipsilesional MEPs and therefore cannot draw the same conclusions for the MA upper limb. The CSP following an excitatory MEP is thought result in a temporary suppression in motor cortical output.[92,94] This suppression of motor cortical output may lead to a decreased inhibitory input to the motoneurone pool, which is thought to increase overall excitability of the corticospinal tract.[92] The first 50 ms of the CSP duration is believed to

be controlled by spinal mechanisms, whereas reductions after 100 ms are assumed to be caused by supraspinal inhibition.[95,96] As the reduction in CSP duration seen in our participants was from 131 ms to 115 ms, it is possible that the training-induced reduction in inhibition was due primarily to cortical factors, however this reduction in CSP could involve spinal mechanisms as well. Diminished hand function and prolonged CSP durations have been observed in persons with stroke compared to healthy controls,[97] and a reduction in inhibitory influence is believed to be important in post-stroke rehabilitation.[96] Additionally, progressive decreases in CSP duration have accompanied clinical improvements in motor outcomes.[45,98] Therefore, this decrease in corticospinal inhibition could create a beneficial environment for upper limb motor rehabilitation in chronic stroke. Further work is needed with a sample with measurable CSPs on the ipsilesional, untrained hemisphere for these possible benefits to be considered attributable to both limbs.

Transcallosal inhibition offers us information about the biology of motor recovery after chronic stroke in individuals with mild to severe arm impairment.[78] Importantly, this can provide stroke researchers and clinicians with great detail regarding an optimal environment for post-stroke rehabilitation. Our research shows a significant decrease in TCI from both hemispheres after a five-week unilateral MVIC strength training intervention. Harris-Love et al.[47,99] found that an increase in inhibition as indexed by iSP from the contralesional to the ipsilesional hemisphere was associated with more severe impairment according to FM scores. Further, increases in reaching ability of the MA arm were accompanied by a decreased CL-iSP.[47,99] Other models of cortical excitability after stroke states that motor deficits may be related to an imbalance of the amount of

interhemispheric inhibition, with the ipsilesional hemisphere having less TCI than the contralesional hemisphere,[38,43,100] these models assume that recovery is related to balancing these levels of TCI. However, this recovery due to balanced levels of TCI may not be the case in individuals with severe stroke (FM < 28).[90] Hayward et al. (in review) showed that a reduction in inhibition indexed with TCI from the ipsilesional hemisphere to the contralesional hemisphere was related to better motor function in a sample of 29 severe stroke participants.[101] Data from the current study and Hayward et al. suggests that a decrease in TCI from both hemispheres may contribute to a global state of decreased inhibition in the motor cortices, thus providing a beneficial environment for increased bilateral strength and improved in motor function.

Despite the effects of the present strength training intervention on other measures of cortical inhibition (CSP, TCI), the current research does not show the decreases in SICI seen in other cross-education studies in healthy individuals.[50,92] This could be due to the fact that we performed post-intervention TMS testing four days after the last training session, whereas these studies performed on the final day of training. It is possible that training-induced effects on SICI were present but not long lasting,[50,92] and future studies should perform post-intervention TMS immediately after study completion. Additionally, we could only perform paired-pulse TMS protocols in 4/12 participants due to the lack of a MEP. Another explanation could be that corticospinal and intracortical changes underlying cross-education could be different in persons with chronic stroke than healthy individuals, as we recorded changes in corticospinal inhibition and interhemispheric inhibition using different protocols.

Aim 3: Changes in motor function or impairment

Improvements were seen in the Upper-Extremity Fugl-Meyer and the WMFT for both the LA (trained) and MA (untrained) arm following training. This suggests that upper-extremity motor impairment decreased following this intervention, and upper-extremity motor function improved. It has been suggested that a minimal improvement score for this test is required to show clinical change, however there is no universally agreed upon minimal clinically important difference (MCID) for Fugl-Meyer. Studies in chronic stroke have shown that the MCID could be anywhere from 4.25-7.25, and studies in subacute stroke have shown it to be 9. These studies have examined individuals with mild to moderate impairment. In the current study the average FM increase was 2.5, with 5 participants increasing their score by more then 4 points. It is possible that in a more severe stroke sample a smaller change is needed to produce a clinical difference. As this was a 5-week intervention, and individuals retained their FM improvement after a 5-week retention period, cross-education may have the potential to decrease upper-extremity impairment in chronic stroke. However, further research is needed to assess the impact of these changes on activities of daily living.

After the intervention individuals significantly improved WMFT values for both sides. This suggests an improvement in motor function over the course of the cross-education intervention. Lin et al. (2009) investigated clinically important differences in WMFT post stroke, and these values were based on WMFT time. They found that for an improvement to be clinically important it had to improve by 14-30%. The current study used WMFT rate, proportional to the time (WMFT rate = 60/time), therefore similar percentage gains should show clinical change. Participants improved by an average of

17% on the LA (trained) arm and 37% on the MA (untrained) arm, showing that this type of intervention has the potential to improve upper extremity motor function as indexed by the WMFT. This improvement was not retained after the 5-weeks without training, suggesting that training or different rehabilitation has to continue to retain these changes in function. Further research is needed to determine the effects of cross-education on upper limb function and activities of daily living.

2.5 Conclusions

In conclusion, data from this thesis support other evidence showing that a unilateral, cross-education strength training intervention in individuals with chronic stroke can yield bilateral gains in strength[13], and that this training is successful in the upper limb. Furthermore, we provide evidence of changes in corticospinal inhibition and transcallosal inhibition underlying these strength gains, possibly contributing to the increases in upper limb function and decreases in impairment that occurred post-intervention. Not only does this research show that these adaptations are possible post stroke, but that they are possible years after infarct (avg. PSD = 128 months) in a severe stroke sample, with a relatively minimal training intervention that is easily accessible and can be performed at home. Further work should explore changes in strength gains, corticospinal and intracortical circuits, and clinical outcome measures, in differing degrees of stroke severity to determine if the changes occurring differ by severity, so that the training intervention can be optimized per person. Continuing efforts must also examine a larger sample size with ipsilesional MEPs to determine the effects of this training in both cortical hemispheres, as well as using different neuroimaging techniques

(e.g. MRI) to uncover more effects of unilateral strength training of the LA limb on specific neural circuits and brain structures.

3 Conclusions and General Discussion

3.1 Introduction

The purpose of the present thesis was to determine the effects of five weeks MVIC training of the non-paretic (LA) wrist extensor muscles on bilateral gains in strength, corticospinal and intracortical adaptations, and clinical outcome measures of function and impairment, in chronic stroke. The strength training consisted of 25-minute sessions, 3 times per week, for 5 weeks. One strength training session was performed in the laboratory and 2 at home per week. Participants' strength, neurophysiological, and clinical outcome measures were compared between 3 time-points: T_0 (average of 3 baselines, separated by 4 days), T_1 (post 5-weeks with strength-training intervention), and T_2 (post 5-weeks with no strength-training intervention).

In the experiment (**Chapter 2)**, 24 individuals with chronic (> 6 months post-stroke) stroke completed 3 baseline sessions consisting of wrist extensor MVIC testing, TMS collection, and clinical measure testing. These sessions were separated by 4-7 days. Following baseline testing, participants performed 5x5 (sets x repetitions) wrist extensor MVIC contractions, held for 5 seconds with 3 seconds rest, 3 times a week. Participants came in 4 days after the final training bout to repeat measures collected in the baseline sessions, and 5-weeks after the post-intervention date to repeat measures a final retention test. TMS measures collected were corticomotoneuronal excitability and inhibition, SICI, ICF, and TCI.

We hypothesized that undergoing a 5-week MVIC strength training intervention of the non-paretic (LA) wrist extensors would improve strength bilaterally relative to

baseline. Likewise, we hypothesized that this intervention would significantly increase corticospinal excitability and ICF, reduce corticospinal inhibition and SICI, as well as improve function and reduce impairment as indexed by our clinical outcome measures. The results of this experiment are summarized and discussed in the current chapter.

3.2 Summary of Findings

3.2.1 The Effect of Unilateral Strength Training of the Wrist Extensors on Corticospinal and Strength Adaptations After Stroke.

Existing work from the Rehabilitation Neuroscience Laboratory at UVIC[13] showed that unilateral strength training of the non-paretic (LA) dorsiflexors can improve strength bilaterally ("cross-educate") in a chronic stroke population. This work showed that the "cross-education" phenomenon in stroke has a more robust effect as compared to healthy individuals, perhaps due to individuals with stroke being detrained in comparison to healthy controls,[102] and the use of a novel strength training task.[17] Cross-education work in healthy individuals has been accompanied by neurophysiological changes such as a decrease in corticospinal inhibition,[92] an increase in corticospinal excitability,[55] and decreases in SICI.[92] These neurophysiological conditions could present a beneficial environment for improved motor function in stroke rehabilitation.[66,67,97] A unilateral MVIC strength training intervention of the non-paretic (LA) upper limb, accompanied by neurophysiological TMS measurements had not been researched in chronic stroke. The present work (**Chapter 2)** aimed to examine the effects of this type of intervention in a sample of individuals with chronic stroke.

Results from the present experiment (**Chapter 2**) demonstrated that the cross-

education effect is present and robust in the upper-limb of individuals with chronic stroke, and that individuals with severe stroke have the capacity to increase strength in their paretic (MA) arm. We found that this training was accompanied by a possible decrease in $GABA_B$-mediated inhibition[103], as indexed by a shortened CSP duration[104], and a reduction in TCI of both hemispheres, as well as an improvement in function and decrease in impairment, measured by the WMFT and FM, respectively. We interpreted that these neurophysiological changes may underlie the bilateral gain in strength and create an optimal environment for rehabilitation post-stroke.[47,96,99]

3.3 Limitations

There were several limitations inherent in the current thesis. The first was the inability to elicit an ipsilesional MEP in 5/12 participants, and unable to elicit a TS for paired-pulse TMS with enough amplitude[82] in 7/12 participants. The net result of absent MEPs in many from our sample is a lack of data for recruitment curves, CSPs, or paired-pulse TMS, for the ipsilesional hemisphere, paretic (MA) arm. As such, it will be important for future research to examine cross-education training in a sample of individuals with stroke who have ipsilesional MEPs. However, studying individuals who do have MEP's on the ipsilesional side may represent and entirely different set of people with stroke as they are likely to not be as severely affected by their stroke.[57,105] In addition, people with less severe stroke may not be the individuals suited to gain the most from cross-education training.

A second limitation is that our inclusion criteria only specified that an individual have pronounced hemiparetic loss of function, but were not restricted to a particular level

of function. Therefore, we cannot state that our intervention explicitly targets one level of stroke severity. Further work should research cross-education interventions with samples of different levels of stroke severity.

Finally, the strength training device given to participants could only be turned on to record sessions, and strapped to their arm if this person was able to reach the device with their paretic arm, or had someone around to help them twice a week. One participant travelled to the laboratory for every training session. As this did not affect the results, it is more of a convenience issue for the participant, as s/he had to devote more of their time to the current study. Going forward devices should be constructed so they are able to be activated and used with just the non-paretic arm so the study can be more inclusive.

3.4 Conclusion and Future Directions

The current thesis has described multiple paths for future research considerations. In particular, continuing efforts should include a larger sample size of individuals with ipsilesional MEPs in order to discover how intracortical and corticospinal networks adapt to cross-educational strength training interventions. MRI studies have previously looked at cortical changes associated with cross-education,[17] but have yet to be researched in a stroke population. Gathering further neurophysiological information underlying cross-educational training in stroke could provide researchers and clinicians with important information regarding beneficial states for neural and motor rehabilitation. Future research could pair unilateral MVIC strength training with paired associated stimulation and motor learning tasks to determine whether combining these interventions could be used to prime a stroke participant for neuroplasticity. Finally, additional research could

combine cross-education of upper and lower limb muscle groups to see if this maximizes rehabilitation potential in individuals with severe stroke.

Presently, motor disabilities related to stroke diminish the quality of life for many individuals and cause a major economic burden. Despite the presence of multiple accepted post-stroke rehabilitation interventions, many individuals are either too severely affected, cannot afford to take part in, or do not have access to the appropriate clinicians or equipment. Cross-educational strength training can benefit these individuals immensely as it requires minimal equipment, is inexpensive, and can be performed in the participant's home. The benefits of this relatively new field of stroke research are numerous and promising, with the potential to make a positive difference in the lives of many individuals living with stroke-related disabilities.

References

1. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update. *Clin Neurophysiol*. 2011;122(8):1686. doi:10.1016/j.clinph.2010.12.037.

2. Canadian Society for Exercise Physiology (CSEP). Physical activity readiness questionnaire - PAR-Q. 2002.

3. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med*. 1AD;7(1):13.

4. Wolf SL, Catlin P a., Ellis M, Archer a. L, Morgan B, Piacentino a. Assessing Wolf Motor Function Test as Outcome Measure for Research in Patients After Stroke. *Stroke*. 2001;32(7):1635-1639. doi:10.1161/01.STR.32.7.1635.

5. Berg K. Measuring balance in the elderly: Development and validation of an instrument. *Can J Public Heal*. 1992;(May):1-130. doi:10.1016/j.archger.2009.10.008.

6. Krueger H, Koot J, Hall RE, O'Callaghan C, Bayley M, Corbett D. Prevalence of Individuals Experiencing the Effects of Stroke in Canada: Trends and Projections. *Stroke*. 2015;46(8):2226-2231. doi:10.1161/STROKEAHA.115.009616.

7. Boyd L a, Winstein CJ. Explicit Information Interferes with Implicit Motor Learning of Both Continuous and Discrete Movement Tasks After Stroke. *J Neurol Phys Ther*. 2006;30(2):46-57. doi:10.1097/01.NPT.0000282566.48050.9b.

8. Zorowitz RD. Brain Trauma Stroke Stroke Rehabilitation — An Overview of Existing Guidelines and Standards of Care. 2011:41-45.

9. The New England Journal of Medicine Downloaded from nejm.org on December 12, 2014. For personal use only. No other uses without permission. Copyright © 1993 Massachusetts Medical Society. All rights reserved. 1993.

10. Peppen R Van, Kwakkel G, Wood-Dauphinee S. The impact of physical therapy on functional outcomes after stroke : what ' s the evidence ? *Clin Rehabiliitation*. 2004;18(00):833-862.

11. Wolf SL, Winstein CJ, Miller JP, et al. Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. *Lancet Neurol*. 2008;7(1):33-40. doi:10.1016/S1474-4422(07)70294-6.

12. Page SJ, Sisto S, Levine P, Johnston M V, Hughes M, Orange W. Modified constraint induced therapy : A randomized feasibility and efficacy study. 2001;38(5):583-590.

13. Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. *Exp brain Res*. 2013;225(1):93-104. doi:10.1007/s00221-012-3351-x.

14. Urbin MA, Harris-Love ML, Carter AR, Lang CE. High-Intensity, Unilateral Resistance Training of a Non-Paretic Muscle Group Increases Active Range of Motion in a Severely Paretic Upper Extremity Muscle Group after Stroke. *Front Neurol*. 2015;6(May):119. doi:10.3389/fneur.2015.00119.

15. Farthing JP. Cross-Education of Strength Depends on Limb Dominance : Implications for Theory and Application. 2009;(33):179-187.

16. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. *J Appl Physiol*. 2006;101(5):1514-1522. doi:10.1152/japplphysiol.00531.2006.

17. Farthing J, Borowsky R, Chilibeck P. Neuro-physiological adaptations associated with cross-education of strength. *J Appl Physiol*. 2007:77-88. doi:10.1007/s10548-007-0033-2.

18. Farthing JP, Zehr EP. Restoring Symmetry : Clinical Applications of Cross-Education. *Am Coll Sport Med*. 2014.

19. Dragert K, Zehr EP. Bilateral neuromuscular plasticity from unilateral training of the ankle dorsiflexors. *Exp brain Res*. 2011;208(2):217-227. doi:10.1007/s00221-010-2472-3.

20. Munn J, Herbert RD, Hancock MJ, Gandevia SC. Training with unilateral resistance exercise increases contralateral strength. *J Appl Physiol*. 2005;99(5):1880-1884. doi:10.1152/japplphysiol.00559.2005.

21. Munn J, Herbert RD, Gandevia SC. Contralateral effects of unilateral resistance training: a meta-analysis. *J Appl Physiol*. 2004;96(5):1861-1866. doi:10.1152/japplphysiol.00541.2003.

22. Farthing JP, Krentz JR, Magnus CRA. Strength training the free limb attenuates strength loss during unilateral immobilization Strength training the free limb attenuates strength loss during unilateral immobilization. *J Appl Physiol*. 2014;(January 2009):830-836. doi:10.1152/japplphysiol.91331.2008.

23. Farthing JP, Chilibeck PD, Binsted G. Cross-Education of Arm Muscular Strength Is Unidirectional in Right-Handed Individuals. *Med Sci Sport Exerc*. 2005;37(9):1594-1600. doi:10.1249/01.mss.0000177588.74448.75.

24. Lagerquist O, Zehr EP, Docherty D. Increased spinal reflex excitability is not associated with neural plasticity underlying the cross-education effect. *J Appl Physiol*. 2006;100(1):83-90. doi:10.1152/japplphysiol.00533.2005.

25. Ehrsson HH, Fagergren A, Jonsson T, et al. Cortical Activity in Precision- Versus Power-Grip Tasks : An fMRI Study Cortical Activity in Precision- Versus Power-Grip Tasks : An fMRI Study. 2014:528-536.

26. Gerardin E, Sirigu A, Lehéricy S, et al. Partially Overlapping Neural Networks for Real and Imagined Hand Movements. 2000:1093-1104.

27. Morris SL, Dodd KJ, Morris ME. Outcomes of progressive resistance strength training following stroke: a systematic review. *Clin Rehabil*. 2004;18(1):27-39. doi:10.1191/0269215504cr699oa.

28. Zehr EP, Barss TS, Kaupp C, et al. Replace, Repair, Restore, Relieve – Bridging Clinical and Engineering Solutions in Neurorehabilitation. Jensen W, Andersen OK, Akay M, eds. 2014;7:219-225. doi:10.1007/978-3-319-08072-7.

29. Zehr EP, Loadman PM, Hundza SR. Neural control of rhythmic arm cycling after stroke. *J Neurophysiol*. 2012;108(3):891-905. doi:10.1152/jn.01152.2011.

30. Rothwell J. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods*. 1997;74(2):113-122. doi:10.1016/S0165-0270(97)02242-5.

31. Chen R, Tam A, Bütefisch C, et al. Intracortical Inhibition and Facilitation in Different Representations of the Human Motor Cortex Intracortical Inhibition and Facilitation in Different Representations of the Human Motor Cortex. 2014:2870-2881.

32. Hallett M. Transcranial magnetic stimulation and the human brain. 2000;406(July):147-150.

33. Auriat AM, Neva JL, Peters S, Ferris JK, Boyd LA. A review of transcranial magnetic stimulation and multimodal neuroimaging to characterize post-stroke neuroplasticity. *Front Neurol*. 2015;6(OCT):1-20. doi:10.3389/fneur.2015.00226.

34. Delvaux V, Alagona G, Gérard P, De Pasqua V, Pennisi G, De Noordhout AM. Post-stroke reorganization of hand motor area: A 1-year prospective follow-up with focal transcranial magnetic stimulation. *Clin Neurophysiol*. 2003;114(7):1217-1225. doi:10.1016/S1388-2457(03)00070-1.

35. Trompetto C, Assini a, Buccolieri a, Marchese R, Abbruzzese G. Motor recovery following stroke: a transcranial magnetic stimulation study. *Clin Neurophysiol*. 2000;111(10):1860-1867. doi:10.1016/S1388-2457(00)00419-3.

36. Traversa R, Cicinelli P, Pasqualetti P, Filippi M, Rossini PM. Follow-up of interhemispheric differences of motor evoked potentials from the "affected" and "unaffected" hemispheres in human stroke. *Brain Res*. 1998;803(1-2):1-8. doi:10.1016/S0006-8993(98)00505-8.

37. Ahonen JP, Jehkonen M, Dastidar P, Molnár G, Häkkinen V. Cortical silent period evoked by transcranial magnetic stimulation in ischemic stroke. *Electroencephalogr Clin Neurophysiol - Electromyogr Mot Control*. 1998;109(3):224-229. doi:10.1016/S0924-980X(98)00014-9.

38. Shimizu T, Hosaki A, Hino T, Sato M, Komori T. Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. *Brain*. 2002. http://brain.oxfordjournals.org/content/125/8/1896.short. Accessed December 11, 2014.

39. Liepert J, Storch P, Fritsch a, Weiller C. Motor cortex disinhibition in acute stroke. *Clin Neurophysiol*. 2000;111(4):671-676. doi:10.1016/S1388-2457(99)00312-0.

40. Edwards JD, Meehan SK, Linsdell M a, et al. Changes in thresholds for intracortical excitability in chronic stroke: more than just altered intracortical inhibition. *Restor Neurol Neurosci*. 2013;31(6):693-705. doi:10.3233/RNN-120300.

41. Cicinelli P, Pasqualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. *Stroke*. 2003;34(11):2653-2658. doi:10.1161/01.STR.0000092122.96722.72.

42. Wittenberg GF, Chen R, Ishii K, et al. Constraint-Induced Therapy in Stroke: Magnetic-Stimulation Motor Maps and Cerebral Activation. *Neurorehabil Neural Repair*. 2003;17(1):48-57. doi:10.1177/0888439002250456.

43. Murase N, Duque J, Mazzocchio R, Cohen LG. Murase 2004, annals of neurology, interhem interaction. 2004:400-409.

44. Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG. Transcallosal inhibition in chronic subcortical stroke. *Neuroimage*. 2005;28(4):940-946. doi:10.1016/j.neuroimage.2005.06.033.

45. Traversa R, Cicinelli P, Oliveri M, et al. Neurophysiological follow-up of motor cortical output in stroke patients. *Clin Neurophysiol*. 2000;111(9):1695-1703. doi:10.1016/S1388-2457(00)00373-4.

46. Honaga K, Fujiwara T, Tsuji T, Hase K, Ushiba J, Liu M. State of intracortical inhibitory interneuron activity in patients with chronic stroke. *Clin Neurophysiol*. 2013;124(2):364-370. doi:10.1016/j.clinph.2012.08.005.

47. Harris-Love ML, Chan E, Dromerick AW, Cohen LG. Neural Substrates of Motor Recovery in Severely Impaired Stroke Patients With Hand Paralysis. *Neurorehabil Neural Repair*. 2015:1545968315594886 - . doi:10.1177/1545968315594886.

48. Berardelli A, Abbruzzese G, Chen R, et al. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. *Brain Stimul*. 2008;1(3):183-191. doi:10.1016/j.brs.2008.06.005.

49. Stinear CM, Barber PA, Coxon JP, Verryt TS, Acharya PP, Byblow WD. Repetitive stimulation of premotor cortex affects primary motor cortex excitability and movement preparation. *Brain Stimul*. 2009;2:152-162. doi:10.1016/j.brs.2009.01.001.

50. Goodwill AM, Pearce AJ, Kidgell DJ. Corticomotor plasticity following unilateral strength training. *Muscle Nerve*. 2012;46(3):384-393. doi:10.1002/mus.23316.

51. Latella C, Kidgell DJ, Pearce AJ. Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. *Eur J Appl Physiol*. 2012;112(8):3097-3107. doi:10.1007/s00421-011-2289-1.

52. Weier a T, Pearce a J, Kidgell DJ. Strength training reduces intracortical inhibition. *Acta Physiol (Oxf)*. 2012;206(2):109-119. doi:10.1111/j.1748-1716.2012.02454.x.

53. Stedman A, Davey N, Ellaway P. Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous. *J Appl Physiol*. 1998;(August):1033-1039. http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-4598(199808)21:8<1033::AID-MUS7>3.0.CO;2-9/abstract. Accessed October 31, 2014.

54. Griffin L, Cafarelli E. Transcranial magnetic stimulation during resistance training of the tibialis anterior muscle. *J Electromyogr Kinesiol*. 2007;17:446-452. doi:10.1016/j.jelekin.2006.05.001.

55. Perez M a, Cohen LG. Scaling of motor cortical excitability during unimanual force generation. *Cortex*. 2009;45(9):1065-1071. doi:10.1016/j.cortex.2008.12.006.

56. Takahashi K, Maruyama A, Maeda M, et al. Unilateral grip fatigue reduces short interval intracortical inhibition in ipsilateral primary motor cortex. *Clin Neurophysiol*. 2009;120(1):198-203. doi:10.1016/j.clinph.2008.10.003.

57. Liepert J, Hamzei F, Weiller C. MOTOR CORTEX DISINHIBITION OF THE UNAFFECTED HEMISPHERE AFTER ACUTE STROKE. *Muscle Nerve*. 2000;(November):1761-1763. http://onlinelibrary.wiley.com/doi/10.1002/1097-4598(200011)23:11<1761::AID-MUS14>3.0.CO;2-M/abstract. Accessed December 2, 2014.

58. Farthing JP, Chilibeck PD, Binsted G. Cross-Education of Arm Muscular Strength Is Unidirectional in Right-Handed Individuals. *Med Sci Sport Exerc*. 2005;37(9):1594-1600. doi:10.1249/01.mss.0000177588.74448.75.

59. Brown K, Neva J, Ledwell N, Boyd LA. Use of transcranial magnetic stimulation in the treatment of selected movement disorders. *Degener Neurol Neuromuscul Dis*. 2014;4:133-151.

60. Wittenberg GF, Chen R, Ishii K, et al. Constraint-Induced Therapy in Stroke: Magnetic-Stimulation Motor Maps and Cerebral Activation. *Neurorehabil Neural Repair*. 2003;17(1):48-57. doi:10.1177/0888439002250456.

61. Veerbeek JM, Van Wegen E, Van Peppen R, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS One*. 2014;9(2). doi:10.1371/journal.pone.0087987.

62. Ehrensberger M, Simpson D, Broderick P, Monaghana K. Cross-education of strength has a positive impact on post-stroke rehabilitation: a systematic literature review. *Top stroke*. 2016;23(2):126-135. doi:10.1080/10749357.2015.1112062.

63. Ekstrand E, Lexell J, Brogårdh C. Grip strength is a representative measure of muscle weakness in the upper extremity after stroke. *Top Stroke Rehabil*. 2016;9357(May):1-6. doi:10.1080/10749357.2016.1168591.

64. Pearce AJ, Thickbroom GW, Byrnes ML, Mastaglia FL. Functional reorganisation of the corticomotor projection to the hand in skilled racquet players. *Exp Brain Res*. 2000;130:238-243. doi:10.1007/s002219900236.

65. Hummel F. Improvement of Motor Function with Noninvasive Cortical Stimulation in a Patient with Chronic Stroke. *Neurorehabil Neural Repair*. 2005;19(1):14-19. doi:10.1177/1545968304272698.

66. Liuzzi G, H??rni?? V, Lechner P, et al. Development of movement-related intracortical inhibition in acute to chronic subcortical stroke. *Neurology*. 2014;82(3):198-205. doi:10.1212/WNL.0000000000000028.

67. Kim YK, Yang EJ, Cho K, Lim JY, Paik N-J. Functional Recovery After Ischemic Stroke Is Associated With Reduced GABAergic Inhibition in the Cerebral Cortex: A GABA PET Study. *Neurorehabil Neural Repair*. 2014;28:576-583. doi:10.1177/1545968313520411.

68. Sullivan KJ, Tilson JK, Cen SY, et al. Fugl-meyer assessment of sensorimotor function after stroke: Standardized training procedure for clinical practice and clinical trials. *Stroke*. 2011;42(2):427-432. doi:10.1161/STROKEAHA.110.592766.

69. Podsiadlo D, Richardson S. The Timed Up and Go - A Test of Basic Functional Mobility For Frail Elderly Persons. *J Am Geriatr Soc*. 1991;39(2):142-148.

70. Enright PL, McBurnie MA, Bittner V, et al. The 6-min walk test: A quick measure of functional status in elderly adults. *Chest*. 2003;123(2):387-398. doi:10.1378/chest.123.2.387.

71. Bird SP, Tarpenning KM, Marino FE. Programmes to Enhance Muscular Fitness A Review of the Acute Programme Variables. *Sports Medicine*. 2005;35(10):841-851.

72. Leis A, Trapani V. *Atlas of Electromyography*. Oxford University Press; 2000:224.

73. Rossini PM, Barker a T, Berardelli a, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol*. 1994;91(2):79-92.

74. Ziemann U, Paulus W, Nitsche M a, et al. Consensus: Motor cortex plasticity protocols. *Brain Stimul*. 2008;1(3):164-182. doi:10.1016/j.brs.2008.06.006.

75. Chen R. Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res*. 2004;154(1):1-10.

76. Möller C, Arai N, Jöorg L, Ziemann U. Hysteresis effects on the input-output curve of motor evoked potentials. *Clin Neurophysiol*. 2009;120:1003-1008.

77. Mang CS, Snow NJ, Campbell KL, Ross CJD, Boyd LA. A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning. *J Appl Physiol*. 2014;117(11):1325-1336. doi:10.1152/japplphysiol.00498.2014.

78. Mang CS, Brown KE, Neva JL, Snow NJ, Campbell KL, Boyd LA. Promoting Motor Cortical Plasticity with Acute Aerobic Exercise: A Role for Cerebellar Circuits. *Neural Plast*. 2016;2016:6797928. doi:10.1155/2016/6797928.

79. Rosenkranz K, Kacar A, Rothwell JC. Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. *J Neurosci*. 2007;27(44):12058-12066. doi:10.1523/JNEUROSCI.2663-07.2007.

80. Mang CS, Borich MR, Brodie SM, et al. Diffusion imaging and transcranial magnetic stimulation assessment of transcallosal pathways in chronic stroke. *Clin Neurophysiol*. 2015;126(10):1959-1971. doi:10.1016/j.clinph.2014.12.018.

81. Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in the human motor cortex. *J Physiol*. 1993;471:501-519.

82. Perez MA, Cohen LG. Mechanisms Underlying Functional Changes in the Primary Motor Cortex Ipsilateral to an Active Hand. *J Neuroscience.* 2008;28(22):5631-5640. doi:10.1523/JNEUROSCI.0093-08.2008.

83. Terao Y, Ugawa Y. Basic mechanisms of TMS. *J Clin Neurophysiol*. 2002;19(4):322-343.

84. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. *Neurorehabilitation & Neural Repair.* 2002;16(3):232-40.

85. Meehan SK, Dao E, Linsdell MA, Boyd LA. Continuous theta burst stimulation over the contralesional sensory and motor cortex enhances motor learning post-stroke. *Neurosci Lett*. 2011;500(1):26-30. doi:10.1016/j.neulet.2011.05.237.

86. Barzi Y, Zehr EP. Rhythmic arm cycling suppresses hyperactive soleus H-reflex amplitude after stroke. *Clin Neurophysiol*. 2008;119(6):1443-1452. doi:10.1016/j.clinph.2008.02.016.

87. Patten C, Lexell J, Brown HE. Weakness and strength training in persons with poststroke hemiplegia: rationale, method, and efficacy. *J Rehabil Res Dev*. 2004;41(3A):293-312. doi:10.1682/JRRD.2004.03.0293.

88. Manca A, Pisanu F, Ortu E, et al. A comprehensive assessment of the cross-training effect in ankle dorsiflexors of healthy subjects: A randomized controlled study. *Gait Posture*. 2015;42(1):1-6. doi:10.1016/j.gaitpost.2015.04.005.

89. Hubal MJ, Gordish-Dressman H, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc*. 2005;37(6):964-972. doi:10.1249.01.mss.0000170469.90461.5f.

90. Dobkin BH, Carmichael ST. The Specific Requirements of Neural Repair Trials for Stroke. *Neurorehabil Neural Repair*. 2015. doi:10.1177/1545968315604400.

91. Liepert J. Motor Cortex Excitability in Stroke Before and After Constraint-induced Movement Therapy. *Cogn Behav Neurol*. 2006;19(1):41-47. doi:10.1097/00146965-200603000-00005.

92. Kidgell DJJ, a.K. Frazer, Rantalainen T, et al. Increased cross-education of muscle strength and reduced corticospinal inhibition following eccentric strength training. *Neuroscience*. 2015;300:566-575. doi:10.1016/j.neuroscience.2015.05.057.

93. Kidgell DJ, Stokes MA, Pearce AJ. Strength Training of One Limb Increases Corticomotor Excitability Projecting to the Contralateral Homologous Limb. *Motor Control*. 2011;15(2004):247-266.

94. Lang N, Sueske E, Hasan A, Paulus W, Tergau F. Pregabalin exerts oppositional effects on different inhibitory circuits in human motor cortex: A double-blind, placebo-controlled transcranial magnetic stimulation study. *Epilepsia*. 2006;47(5):813-819. doi:10.1111/j.1528-1167.2006.00544.x.

95. Inghillerj M, Berardelli A, Cruccu G, Manfredi M. Silent Period Evoked By Transcranial Stimulation of the Human Cortex and Cervicomedullary Junction. *J Physiol*. 1993;466:521-534. doi:10.1113/jphysiol.1993.sp019732.

96. Van Kuijk A a, Pasman JW, Geurts ACH, Hendricks HT. How salient is the silent period? The role of the silent period in the prognosis of upper extremity motor recovery after severe stroke. *J Clin Neurophysiol*. 2005;22(1):10-24. doi:10.1097/01.WNP.0000150975.83249.71.

97. Brouwer BJ, Schryburt-Brown K. Hand Function and Motor Cortical Output Poststroke: Are They Related? *Arch Phys Med Rehabil*. 2006;87(5):627-634. doi:10.1016/j.apmr.2006.02.006.

98. Classen J, Schnitzler A, Binkofski F, et al. The motor syndrome associated with exaggerated inhibition within the primary motor cortex of patients with hemiparetic stroke. 1997:605-619.

99. Harris-Love ML, Morton SM, Perez MA, Cohen LG. Mechanisms of short-term training-induced reaching improvement in severely hemiparetic stroke patients: a TMS study. *Neurorehabil Neural Repair*. 2011;25(5):398-411. doi:10.1177/1545968310395600.

100. Boroojerdi B, Diefenbach K, Ferbert A. Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. *J Neurol Sci*. 1996;144(1-2):160-170. doi:10.1016/S0022-510X(96)00222-5.

101. Hayward K, Neva J, Peters S, et al. Characterising Arm Recovery in People with Severe Stroke. *Under Rev*.

102. Zehr EP. Evidence-based risk assessment and recommendations for physical activity clearance: stroke and spinal cord injury. *Appl Physiol Nutr Metab*. 2011;36 Suppl 1:S214-S231. doi:10.1139/h11-055.

103. Lang CE, Beebe JA. Relating Movement Control at 9 Upper Extremity Segments to Loss of Hand Function in People with Chronic Hemiparesis. *Neurorehabil Neural Repair*. 2007;21(3):279-291. doi:10.1177/1545968306296964.

104. Priori A, Berardelli A, Inghilleri M, Polidori L, Manfredi M. Electromyographic silent period after transcranial brain stimulation in Huntington's disease. *Mov Disord*. 1994;9:178-182.

105. Blicher J, Jakobsen J. Cortical excitability in chronic stroke and modulation by training: a TMS study. *Neural Repair*. 2009:486-493. http://nnr.sagepub.com/content/23/5/486.short. Accessed December 11, 2014.

Appendices

Appendix A: Screening Questionnaire Before TMS: An Update.[1]

BRAIN BEHAVIOR LAB
TRANSCRANIAL MAGNETIC STIMULATION (TMS) SCREENING FORM

Below is a questionnaire used to exclude participants considered not suitable for transcranial magnetic stimulation (TMS). This information, as well as your identity, will be kept confidential.
PLEASE COMPLETE FORM BELOW:

Participant Code: _____

Please **CIRCLE ONE**:

Neurological or Psychiatric Disorder	YES	NO	Multiple Sclerosis	YES	NO
Head Trauma	YES	NO	Depression	YES	NO
Stroke	YES	NO	Clinical Depression	YES	NO
Brain surgery	YES	NO	Treatment with amitryptiline and haloperidol	YES	NO
Metal in cranium	YES	NO	Implanted medication pump	YES	NO
Brain Lesion	YES	NO	Intracranial Pathology	YES	NO
Pacemaker	YES	NO	Albinism	YES	NO
History of seizure	YES	NO	Intractable anxiety	YES	NO
Family history of epilepsy	YES	NO	Pregnant	YES	NO
History of epilepsy	YES	NO	Headaches or Hearing problems	YES	NO
Intracorporal electronic devices	YES	NO	Family History of Hearing Loss	YES	NO
Intracardic lines	YES	NO	Other medical conditions	YES	NO

If you answered "yes" to any of the above questions, please provide details below.

_____
_____

Appendix B: Physical Activity Readiness Questionnaire (PAR-Q).[2]

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	1. **Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2. **Do you feel pain in your chest when you do physical activity?**
☐	☐	3. **In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4. **Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5. **Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6. **Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7. **Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE

Appendix C: Fugl-Meyer Upper-Extremity Assessment.[3]

Rehabilitation Medicine, University of Gothenburg

FUGL-MEYER ASSESSMENT **ID:**
UPPER EXTREMITY (FMA-UE) **Date:**
Assessment of sensorimotor function **Examiner:**

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scand J Rehabil Med 1975, 7:13-31.

A. UPPER EXTREMITY, sitting position					
I. Reflex activity			**none**	**can be elicited**	
Flexors: biceps and finger flexors			0	2	
Extensors: triceps			0	2	
Subtotal I (max 4)					
II. Volitional movement within synergies, without gravitational help			**none**	**partial**	**full**
Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination). **Extensor synergy:** Hand from ipsilateral ear to the contralateral knee	Shoulder	retraction	0	1	2
		elevation	0	1	2
		abduction (90°)	0	1	2
		external rotation	0	1	2
	Elbow	flexion	0	1	2
	Forearm	supination	0	1	2
	Shoulder	adduction/internal rotation	0	1	2
	Elbow	extension	0	1	2
	Forearm	pronation	0	1	2
Subtotal II (max 18)					
III. Volitional movement mixing synergies, without compensation			**none**	**partial**	**full**
Hand to lumbar spine	cannot be performed, hand in front of SIAS		0		
	hand behind of SIAS (without compensation)			1	
	hand to lumbar spine (without compensation)				2
Shoulder flexion 0°-90° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion		0		
	abduction or elbow flexion during movement			1	
	complete flexion 90°, maintains 0° in elbow				2
Pronation-supination elbow at 90° shoulder at 0°	no pronation/supination, starting position impossible		0		
	limited pronation/supination, maintains position			1	
	complete pronation/supination, maintains position				2
Subtotal III (max 6)					
IV. Volitional movement with little or no synergy			**none**	**partial**	**full**
Shoulder abduction 0 - 90° elbow at 0° forearm pronated	immediate supination or elbow flexion		0		
	supination or elbow flexion during movement			1	
	abduction 90°, maintains extension and pronation				2
Shoulder flexion 90°- 180° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion		0		
	abduction or elbow flexion during movement			1	
	complete flexion, maintains 0° in elbow				2
Pronation/supination elbow at 0° shoulder at 30°-90° flexion	no pronation/supination, starting position impossible		0		
	limited pronation/supination, maintains extension			1	
	full pronation/supination, maintains elbow extension				2
Subtotal IV (max 6)					
V. Normal reflex activity evaluated only if full score of 6 points achieved on part IV					
biceps, triceps, finger flexors	0 points on part IV or 2 of 3 reflexes markedly hyperactive		0		
	1 reflex markedly hyperactive or at least 2 reflexes lively			1	
	maximum of 1 reflex lively, none hyperactive				2
Subtotal V (max 2)					
Total A (max 36)					

Approved by Fugl-Meyer AR 2010 1

B. WRIST support may be provided at the elbow to take or hold the position, no support at wrist, check the passive range of motion prior testing		none	partial	full
Stability at 15° dorsiflexion elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance is taken maintains position against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Stability at 15° dorsiflexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance is taken maintains position against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Circumduction	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
	Total B (max 10)			

C. HAND support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		none	partial	full
Mass flexion from full active or passive extension		0	1	2
Mass extension from full active or passive flexion		0	1	2
GRASP				
A – flexion in PIP and DIP (digits II-V) **extension in MCP II-V**	cannot be performed can hold position but weak maintains position against resistance	0	1	2
B – thumb adduction 1-st CMC, MCP, IP at 0°, scrap of paper between thumb and 2-nd MCP joint	cannot be performed can hold paper but not against tug can hold paper against a tug	0	1	2
C - opposition pulpa of the thumb against the pulpa of 2-nd finger, pencil, tug upward	cannot be performed can hold pencil but not against tug can hold pencil against a tug	0	1	2
D – cylinder grip cylinder shaped object (small can) tug upward, opposition in digits I and II	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
E – spherical grip fingers in abduction/flexion, thumb opposed, tennis ball	cannot be performed can hold ball but not against tug can hold ball against a tug	0	1	2
	Total C (max 14)			

D. COORDINATION/SPEED after one trial with both arms, blind-folded, tip of the index finger from knee to nose, 5 times as fast as possible		marked	slight	none
Tremor		0	1	2
Dysmetria	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		> 5s	**2 - 5s**	**< 1s**
Time	more than 5 seconds slower than unaffected side 2-5 seconds slower than unaffected side maximum difference of1 second between sides	0	1	2
	Total D (max 6)			

TOTAL A-D (max 66)	

H. SENSATION, upper extremity blind-folded, compared with unaffected side		**anesthesia**	**hypoesthesia dysesthesia**	**normal**
Light touch	upper arm, forearm palmar surface of the hand	0 0	1 1	2 2
		absence less than 3/4 correct	**3/4 correct considerable difference**	**correct 100% little or no difference**
Position small alterations in the position	shoulder elbow wrist thumb (IP-joint)	0 0 0 0	1 1 1 1	2 2 2 2
			Total H (max12)	

J. PASSIVE JOINT MOTION, upper extremity				**J. JOINT PAIN** during passive motion, upper extremity		
Sitting position, compare with unaffected side	only few degrees (less than 10° in shoulder)	decreased	normal	pronounced constant pain during or at the end of movement	some pain	no pain
Shoulder						
Flexion (0° - 180°)	0	1	2	0	1	2
Abduction (0°-90°)	0	1	2	0	1	2
External rotation	0	1	2	0	1	2
Internal rotation	0	1	2	0	1	2
Elbow						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Forearm						
Pronation	0	1	2	0	1	2
Supination	0	1	2	0	1	2
Wrist						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Fingers						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Total (max 24)				**Total** (max 24)		

A. UPPER EXTREMITY	/36
B. WRIST	/10
C. HAND	/14
D. COORDINATION / SPEED	/ 6
TOTAL A-D (motor function)	/66

H. SENSATION	/12
J. PASSIVE JOINT MOTION	/24
J. JOINT PAIN	/24

Appendix D: Wolf Motor Function Test.[4]

Compensatory Brain Activation After Stroke

WOLF MOTOR FUNCTION TEST

Patient ID#:_____

Date:___ ___/___ ___/___ ___ Time: _____

Examiner:_____ Pre-Test ☐

Post Test ☐

Testing Instructions and Scoring

The WMFT consists of 17 tasks performed without the subject's awareness of how the components are defined or scored. All tasks will use both arms, starting with the unaffected arm first. Each task is timed and rated by Functional Ability (0 – 5 Ordinal Scale). Subjects are given a maximum time limit of 120 seconds to complete the assigned task.

Score – Functional Ability

0	Does not attempt with upper extremity (UE) being tested
1	UE being tested does not participate functionally; however, attempt is made to use the UE
2	Does, but requires assistance of the UE not being tested for minor readjustments or changes of position, or requires more than two attempts to complete, or accomplishes very slowly
3	Does, but movement is influenced to some degree by synergy or is performed slowly or with effort
4	Does, movement is close to normal*, but slightly slower; may lack precision, fine coordination or fluidity
5	Does; movement appears to be normal

*Normal – the less involved UE can be utilized as an available index comparison, with pre-morbid UE dominance taken into consideration

Read the follow statement aloud to the patient:

Today we are going to take a look at how you are able to use your arm. Let me tell you how we are going to do this. First, I will give you instructions on how to do the task, and then I will show you how to do it. I will describe and demonstrate each task 2 times. Do not practice the task while I'm describing and demonstrating it. However, I will be happy to clarify any confusing points. Then I will say, "Ready, set, go", and you will do the task. It is important that you do not start until I say "go", otherwise, we will need to repeat the entire task. Each of the activities you will be asked to do should be carried out as rapidly as possible. You can work on each task for up to two minutes. We ask that you attempt each part of the test even if you do not think you can do it. If you are unable to carry out a task, then we will go on to the next one. Again, try to do each task as rapidly as possible. Do you have any questions?

UNAFFECTED HAND

Task	Time	Functional Ability	Comment
1. Forearm to table (side)	_____	0 1 2 3 4 5	_____
2. Forearm to box (side)	_____	0 1 2 3 4 5	_____
3. Extend elbow (side)	_____	0 1 2 3 4 5	_____
4. Extend elbow (weight)	_____	0 1 2 3 4 5	_____
5. Hand to table (front)	_____	0 1 2 3 4 5	_____
6. Hand to box (front)	_____	0 1 2 3 4 5	_____
7. Weight to box	_____	_____ lbs.	_____
8. Reach and retrieve	_____	0 1 2 3 4 5	_____
9. Lift can	_____	0 1 2 3 4 5	_____
10. Lift pencil	_____	0 1 2 3 4 5	_____
11. Lift paper clips	_____	0 1 2 3 4 5	_____
12. Stack checkers	_____	0 1 2 3 4 5	_____
13. Flip cards	_____	0 1 2 3 4 5	_____
~~14. Grip strength~~	_____	_____ kgs.	_____
15. Turn key in lock	_____	0 1 2 3 4 5	_____
16. Fold towel	_____	0 1 2 3 4 5	_____
17. Lift basket	_____	0 1 2 3 4 5	_____

AFFECTED HAND

Task	Time	Functional Ability	Comment
1. Forearm to table (side)	_____	0 1 2 3 4 5	_____
2. Forearm to box (side)	_____	0 1 2 3 4 5	_____
3. Extend elbow (side)	_____	0 1 2 3 4 5	_____
4. Extend elbow (weight)	_____	0 1 2 3 4 5	_____
5. Hand to table (front)	_____	0 1 2 3 4 5	_____
6. Hand to box (front)	_____	0 1 2 3 4 5	_____
7. Weight to box	_____	_____lbs.	_____
8. Reach and retrieve	_____	0 1 2 3 4 5	_____
9. Lift can	_____	0 1 2 3 4 5	_____
10. Lift pencil	_____	0 1 2 3 4 5	_____
11. Lift paper clips	_____	0 1 2 3 4 5	_____
12. Stack checkers	_____	0 1 2 3 4 5	_____
13. Flip cards	_____	0 1 2 3 4 5	_____
14. Grip strength	_____	_____kgs.	_____
15. Turn key in lock	_____	0 1 2 3 4 5	_____
16. Fold towel	_____	0 1 2 3 4 5	_____
17. Lift basket	_____	0 1 2 3 4 5	_____

Clinician Signature

Date: ____ ____ / ____ ____ / ____ ____
Month Day Year

Appendix E: Berg Balance Scale.[5]

Berg Balance Scale

Name: _____ Date: _____

Location: _____ Rater: _____

ITEM DESCRIPTION	SCORE (0-4)
Sitting to standing	_____
Standing unsupported	_____
Sitting unsupported	_____
Standing to sitting	_____
Transfers	_____
Standing with eyes closed	_____
Standing with feet together	_____
Reaching forward with outstretched arm	_____
Retrieving object from floor	_____
Turning to look behind	_____
Turning 360 degrees	_____
Placing alternate foot on stool	_____
Standing with one foot in front	_____
Standing on one foot	_____

Total _____

GENERAL INSTRUCTIONS

Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:

- the time or distance requirements are not met
- the subject's performance warrants supervision
- the subject touches an external support or receives assistance from the examiner

Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing is a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5, and 10 inches. Chairs used during testing should be a reasonable height. Either a step or a stool of average step height may be used for item # 12.

Appendix F: Training Device Instructions.

Preparation

1. Put the wrist extension training device on a flat surface, but don't put arm or any weight on the top of the device for now.
2. Turn on the Power, both GREEN and RED lights will be on, the load cell is zeroing the offset while the RED light is ON,wait till the RED light is OFF.
3. Now, it should be only the GREEN light is ON, you can put your less-affected arm on the device, align your wrist with the trace we drew before, the crease of your wrist should be align with the gaps between two boards.

Warm Up

3 set of 5 repetition, 5 second of each repetition, 50% maximal effort

1. Before beginning, press the RED bottom, RED lights on, now the device start recording data.
2. *Start one set of warm up with 5 repetitions at **50% maximal effort**.*
3. *After finished one set of warm up, press the red button again, stop recording data.*
4. *2mins break*

   Repeat step 1 to 4 till finish **3 sets** of warm up.

Training

5 set of 5 repetition, 5 second of each repetition, 100% maximal effort

1. Before beginning, press the RED bottom, RED lights on, start recording data.
2. *Start 1st set of training with 5 repetitions at **100% maximal effort**.*
3. *After finished one set of training, press the red button again, stop recording data.*
4. *2mins break*

   Repeat step 1 to 4 till finish **5 sets** of training.

After finish the training, turn off the power, GREEN lights OFF