ACUTE LOWER EXTREMITY RESISTANCE EXERCISE AND THE EFFECTS ON CORTICOSPINAL EXCITABILITY IN THE UNEXERCISED UPPER EXTREMITY

by

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Acute Lower Extremity Resistance Exercise and the Effects on Corticospinal Excitability in the Unexercised Upper Extremity

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the degree of Master of Science

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Abstract

Cross-education (CE) of strength occurs when a muscle is trained unilaterally and bilateral improvements in strength are noted. Unilateral resistance exercise can therefore be advantageous for clinical populations, including individuals with stroke, as a means to improve strength bilaterally when only the less affected side of the body can be trained. Yet we do not understand the mechanism through which CE is mediated in the brain, nor do we know if the cortical effects of CE are localized and spatially confined to homologous muscles. The main purpose of the current thesis was to determine the impact of bilateral and unilateral lower extremity (LE) resistance exercise on corticospinal excitability in the unexercised upper extremity (UE).

Twelve healthy participants were recruited to participate in two sessions on separate days. During each session, transcranial magnetic stimulation (TMS) and peripheral nerve stimulation were used to quantify baseline corticospinal excitability in the unexercised UE in the abductor pollicus brevis muscle (APB). This was followed by an acute bout of either a bilateral or unilateral leg extension exercise condition. All participants completed both conditions; the order of the conditions was randomized. Immediately following the acute exercise bout, measures of corticospinal excitability were repeated in the same manner as at baseline. Strength improved in both legs post-exercise in the bilateral (p= 0.042) and unilateral (p=0.005) condition. There was a decrease in intracortical inhibition after bilateral leg extensions were performed in both hemispheres (p=0.05). There were no changes in corticospinal excitability after the unilateral exercise. There were no changes in spinal excitability in either condition in the unexercised UE after LE resistance exercise.

These data suggest that unilateral resistance exercise can improve strength bilaterally. In addition, an acute bout of bilateral LE resistance exercise can influence cortical areas beyond the cortical representation of the exercised limbs. However, acute unilateral resistance exercise bouts may not be able to produce these wide-spread cortical changes to the same extent as bilateral exercise. This current research contributes to the current CE literature, helping to explain the limits of this phenomenon which in turn will facilitate the assimilation of CE into clinical practice.

Lay Summary

Exercise promotes adaptive changes in the brain and can be used to benefit motor outcomes in clinical populations. The current research was conducted to better understand the effect resistance exercise has on the brain, in turn this information can be used to improve clinical interventions for individuals with stroke who have motor deficits. In this study, leg extension exercises were performed using either both or one leg. In order to detect central nervous systems changes as a result of exercise, brain and spinal excitability were measured using brain stimulation and electrical nerve stimulation before and after exercise.

After the resistance exercise there were changes in brain excitability. The current work provides a better understanding of what interventions promote positive brain changes which may improve motor function and quality of life for those with neurological damage.

Preface

The present thesis has been completed by the candidate Kaitlin Attard under the supervision of Dr. Lara Boyd. The experimental design, data processing and analysis and documentation were done primarily through the candidate.

This experiment was done primarily in the Brain Behaviour Laboratory, but equipment and lab space were borrowed from the Motion Analysis and Biofeedback Laboratory under the direction of Dr. Michael Hunt.

This experiment was approved by the University of British Columbia's Research Ethics Board (certificate #H19-00350).

When lab and workspaces re-open following the COVID-19 pandemic, sample size may be increased so that publication can be pursued.

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List of Abbreviations

α-MNs: Alpha motoneuron

APB: Abductor Pollicus Brevis

ANOVA: Analysis of Variance

CE: Cross-Education

CS: Conditioning Stimulus

CSP: Cortical/ Contralateral Silent Period

EMG: Electromyography

GABA: γ- Aminobutyric Acid

$GABA_A$: GABA receptor subtype A

$GABA_B$: GABA receptor subtype B

IHI: Interhemispheric Inhibition

ISI: Interstimulus Interval

iSP: Ipsilateral Silent Period

KG: Kilograms

LE: Lower Extremity

LH: Left Hemisphere

M1: Primary Motor Cortex

MEP: Motor Evoked Potential

ms: millisecond

mV: Millivolt

MVIC: Maximal Voluntary Isometric Contraction

M-wave: Motor Wave

M_{max}: Motor Wave Maximum

Nm: Newton Meters

PAR-Q +: Physical Activity Readiness Questionnaire Plus

RH: Right Hemisphere

rmANOVA: Repeated Measures ANOVA

RMT: Resting Motor Threshold

SD: Standard Deviation

SE: Standard Error

SICI: Short-Interval Intracortical Inhibition

SMA: Supplementary Motor Area

T0: Baseline

T1: Post-exercise

TCI: Transcallosal Inhibition

TMS: Transcranial Magnetic Stimulation

TS: Test Stimulus

UBC: University of British Columbia

UE: Upper Extremity

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Firstly, I would like to thank my supervisor Dr. Lara Boyd for taking me on as a Master's student for the past two years. These years have easily been the most amazing and intellectually stimulating years of my life and this would not have been possible without your constant support and believing in me along with your other students. Thank you for your mentorship.

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To all the participants for this current study as well as other participants for BBL studies. Thank you for giving us your time to help us conduct research and I enjoyed meeting each of you and listening to the stories you would share with me.

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Lastly, a BIG thank you to my friends and family who have provided healthy distractions from my Master's work and supported me every day. I would not be where I am today without the phone calls, hangouts or happy hours we had the past two years.

Dedication

To Megan, Mom, Dad and my friends.

1. Introduction

1.1 Introduction

1.1.1 Background

Hemiparesis is one of the most common deficits and a prevalent cause of disability following a stroke[1]. This deficit leaves individuals with lasting impairments and requires rehabilitation to regain motor function.[2,3,4] Lesions can be present within motor areas making stroke recovery difficult. In healthy individuals, the two motor cortices mutually inhibit one another via connections in the corpus callosum. After stroke, this relationship can become impaired creating interhemispheric imbalance.[5] The primary motor cortex (M1) of the contralesional hemisphere increases the inhibition placed on the lesioned hemisphere, which in turn places less inhibition on the contralesional hemisphere.[6] The magnitude of this relationship has been related to motor function.[7,8] These abnormal patterns of cortical excitability can make motor recovery difficult for individuals as this inhibition impacts use-dependent plasticity after stroke.[5,9,10,11] Therefore, interventions that mitigate this imbalance could be of benefit to individuals after their stroke.

Promoting neuroplasticity can benefit motor recovery by improving inter- and intra-cortical interactions as the cortex changes functionally and structurally with new experiences after cortical damage. Neuroplastic changes that promote increased excitability within the lesioned hemisphere and decreased inhibition from the contralesional to the ipsilesional hemisphere may improve motor function.[12,13,14] Rehabilitation techniques that capitalize on neuroplastic changes to mitigate inhibitory forces to the lesioned hemisphere's M1 can benefit individuals with hemiparetic impairments after stroke to optimize motor outcomes.

Cross-education (CE) is a phenomenon defined as a performance enhancement on the untrained side of the body that occurs after training of the opposite homologous limb.[15,16] Studies show bilateral increases in strength after unilateral exercise coupled with modulation of corticospinal excitability and inhibition.[17,18,19,20] CE could act as a unique strength training intervention to promote neuroplasticity and improve motor function in those with hemiparesis after stroke, but this intervention currently requires further investigation.

1.1.2 What is cross-education?

Cross-education was first described in 1894 by Edward Wheeler Scripture as the phenomenon of bilateral improvements when only training unilaterally.[15] CE has potential as an exercise rehabilitation intervention catered to those with chronic neurological impairments to maintain strength in their affected limb.[21] Cross-education effects on strength are noted in healthy individuals and those with chronic stroke following unilateral resistance exercise.[22,23,24,25] In fact, the effects of CE have even been proven to be exaggerated in those with stroke; this may be due to enhanced capacity for neuroplasticity.[25,26]

The mechanism by which CE is facilitated has yet to be determined. The "cross-activation hypothesis" is the most consistently accepted explanation. This hypothesis states that during unilateral movement, changes in M1 excitability are not contained to the contralateral motor areas but there is bilateral activation of the motor cortices through interhemispheric connections. An alternate hypothesis is the "bilateral access hypothesis" which attributes the cross-over to the brain's ability to learn new motor skills through the storage of motor engrams in the brain after unilateral movements.[27, 28] The cross-activation hypothesis is currently the more accepted, but these two hypotheses may not be mutually exclusive. Bilateral cortical activity may be present during exercise to facilitate interlimb transfer, but this may overlap with motor

information being stored in the trained hemisphere that is then accessible to the other hemisphere after exercise. The degree of involvement that each of these hypotheses have in CE may be dependent on the specific task. There is a global acceptance, however that CE is modulated to some extent through neuroplasticity within the brain that in turn influences bilateral strength gains.[28]

The contralateral transfer of strength to homologous muscles has been shown extensively, demonstrating the reproducibility of the CE.[18,19,29,30] Interhemispheric connections between motor areas allow for cortical motor crossover, so neural information can be shared between hemispheres to excite opposing homologous muscle groups.[31] It has been suggested that activation of the unexercised (ipsilateral) M1 initiates the crossover.[27,32] More specifically, the early reduction in inhibition within ipsilateral M1 is what facilitates a "spillover" effect of corticomotor information.[27] However, the assumption that the motor cortices are the only brain region contributing to CE is incorrect. Human neuroimaging studies have found evidence for the supplementary motor area (SMA) to also be heavily involved in CE. Bilateral SMA activity is prominent during unilateral movements due to pre SMA's dense corpus callosal connections through which corticomotor information can be shared easier between homologous areas facilitating CE.[28,33] Information from diffusion tensor imaging has shown its dense structural connectivity by which homologous SMA areas relay information through this link.[28] Compared to other motor areas such as dorsal premotor cortices and somatosensory cortex, the amount of fibres connecting homologous SMA's appears to be larger. Turner and colleagues in 1998 also discovered that there was facilitated cerebral blood flow to bilateral cerebellar and premotor regions during a right-handed tracking task showing promise for their contribution to CE as well.[34] Currently, the most researched motor area to determine the cortical impact of CE is M1.[28]

The potential contributions of non-cortical regions of the central nervous system to the mechanism of CE have also been investigated. Hoffman-reflex (H-reflex), a reflex elicited through electrical nerve stimulation has shown increased excitability bilaterally reflected through increased H-reflex amplitude after unilateral strength training, suggesting the presence of spinal adaptations during CE in healthy individuals.[35,36,37] Studies that have found increased excitability in the motoneuron pool after unilateral exercise suggest that these changes may be elicited upstream in the motor cortices and not actually originate at the spinal level.[28] This suggests that changes that are seen in spinal excitability may occur as a result of cortical origination, indicating that subcortical structures may not be as important in mediating CE as cortical structures.

1.1.3 Transcranial magnetic stimulation and cross-education

Transcranial magnetic stimulation (TMS) is a non-invasive technique that can probe M1 excitability by quantifying the amplitude of motor evoked potentials (MEP).[38,39] The connectivity between the M1 in the hemispheres can also be assessed, using either dual-coil paired-pulse or single pulse TMS to probe interhemispheric inhibition (IHI).[40] These techniques are surrogate measures of neuroplasticity within M1 when measured before and after interventions. Transcranial magnetic stimulation has been utilized and is safe for both healthy individuals and people with chronic stroke.[17,25,41]

The specific neural adaptations that occur in association with CE are unclear. Resistance exercise has been shown to increase corticospinal excitability post exercise in the exercised muscle.[42] The use of MEPs to quantify changes in corticospinal excitability has been used frequently in unilateral resistance exercise interventions. Even when CE of strength is exhibited, measures of corticospinal excitability, including MEPs, are variable. It appears that measures of

corticospinal excitability following CE may be dependent on the muscle being tested and as such can be inconclusive as an assessment of change in the untrained muscles.[32,43] In contrast, changes in cortical inhibition show more consistent findings. Short interval intracortical inhibition (SICI) is a surrogate measure of gamma-aminobutyric acid- sub type a ($GABA_A$) - receptor related inhibition in M1.[44,45,46] Contralateral silent periods (CSPs) are a reduction in electromyography (EMG) activity following a MEP during active contractions elicited by corticospinal inhibitory circuits regulated by release of $GABA_B$. [44,45] $GABA_A$ and $GABA_B$ mediated inhibition contribute to neuroplasticity within M1. In CE, a reduction in inhibition in the untrained hemisphere acts to send excitatory drive to the untrained muscle allowing strength gains.[30,47] A decrease in $GABA_A$ and $GABA_B$ mediated inhibition fosters net excitability and has been shown following acute and long duration unilateral resistance exercise consistently as a result of CE.[17,43,48,49] A recent meta-analysis suggests these two measures (CSP and SICI) be consistently used to quantify neurophysiological changes in CE research.[43]

Another important but less frequently used measure to quantify cortical inhibition in CE research is IHI which indexes the ability of one hemisphere to inhibit the other through corpus callosal pathways.[50,51] IHI can be mapped through dual-coil paired-pulse paradigms or transcallosal inhibition (TCI).[51,52] Hortobágyi and colleagues specifically investigated whether a reduction in IHI in M1 contributes to task performance gains in the unexercised muscle. They concluded that a reduction in IHI contributed largely to the interlimb transfer that was present and that the magnitude of these interhemispheric changes reflected those seen during performance[32]. Interhemispheric inhibition is quantified by measuring the ipsilateral silent period (iSP) which shows the magnitude of inhibition being placed on one hemisphere by the other and originates from the activation of cortical inhibitory interneurons[44,45]. Theoretically, a reduction in

IHI should facilitate enhanced communication between hemispheres causing bilateral changes in strength after unilateral exercise[,32]. A more important reason to incorporate this measure into CE research came from a meta-analysis that investigated IHI measures and found it to consistently relate changes in intercortical relationships that correlated with increases in strength[43]. This suggests the importance of hemispheric interactions during CE.

1.1.4 The limits of cross-education

Currently, corticospinal excitability during and after bouts of unilateral resistance exercise has been investigated in opposing homologous muscles. Determining whether the effects of adaptation are specifically localized or transfer to spread beyond the homologous limb cortical representation has been sparsely investigated. Existing research proves an intracortical and corticospinal release of inhibition in the cortical representation of trained limbs post-resistance exercise.[53,54] Beyond this direct transfer between contralateral homologous limbs, there is evidence for this transfer to be less spatially confined and to influence unexercised areas of M1. Singh et al. (2014) found that aerobic exercise on a stationary bike modulated excitability and IHI in the unexercised upper extremity (UE).[55] Neva et al. (2017) verified this result showing that an acute lower extremity (LE) aerobic exercise bout altered the interhemispheric excitability in the unexercised abductor pollicus brevis (APB) muscle. This work demonstrated that a wider portion of M1 was impacted by exercise than just cortical representation of the exercised LE.[56] Takahashi and colleagues found evidence of this cross-body transfer in resistance exercise too when following an exhaustive bilateral leg press bout corticospinal and intracortical excitability were altered in the bilateral unexercised UE. Together, this work illustrates that the neuronal pathways affected by exercise may not be restricted to the pathways of the exercised muscles. [55,56,57]

It is possible that bilateral exercise elicits transfer from the LE to the UE. Past studies investigated performing unilateral muscle contractions or oscillations at the same time as projecting TMS stimulations to a non-homologous muscle to reflect M1 adaptations outside of the localized cortical representation of the trained limb.[58,59] In this research [58,59] bilateral changes in excitability occurred at both a spinal and cortical level in M1 despite non-homologous muscles being investigated. This and other past literature suggest that CE may not be dependent on homologous muscles. Facilitating any voluntary or electrical unilateral muscle activity may elicit widespread bilateral M1 excitation beyond the cortical origin of the adaptation.[58,59,60,61] This suggests the possibility that unilateral resistance exercise in the LE may therefore influence the cortical representation of the unexercised UE in M1.

1.2 Research question, aims and hypotheses

Research Question: What is the impact of lower extremity resistance exercise on corticospinal excitability in the unexercised upper extremity?

Specific Aims

Aim 1: To determine the impact of unilateral lower-limb resistance exercise on strength in the homologous muscle on the opposite limb.

Hypothesis 1: An acute, unilateral bout of lower-limb resistance exercise will increase strength in the opposite leg.

Aim 2: To investigate whether an acute bout of bilateral lower-limb resistance exercise will change bilateral upper extremity corticospinal excitability.

Hypothesis 2: An acute bout of bilateral lower-limb resistance exercise will increase corticospinal excitability in the unexercised upper extremity in both hemispheres.

Aim 3: To investigate whether an acute bout of unilateral lower-limb resistance exercise will change bilateral upper extremity corticospinal excitability.

Hypothesis 3: An acute bout of unilateral lower-limb resistance exercise will increase corticospinal excitability in the unexercised upper extremity in both hemispheres.

1.3 Motivation and rationale

Following stroke, increased IHI from the contralesional to the ipsilesional hemisphere is often present.[6] Increased IHI directed towards the ipsilesional M1 may be associated with poorer motor function.[6,8,62,63] Currently, there is moderate evidence that CE can benefit motor function in individuals with chronic stroke by attempting to normalize IHI.[21] Exercising the less affected limb could improve strength and function bilaterally. Individuals with hemiparesis after stroke could benefit from a unilateral resistance exercise program to provide functional bilateral performance gains and restore symmetry between the less affected and more affected side.[64]

Researching and understanding how to promote interhemispheric communication in healthy individuals through CE is important for determining whether this exercise intervention could be used clinically. CE has the potential to benefit additional corticomotor areas other than the bilateral cortical motor representation of the exercised limb as there is evidence of interactions present between the exercised LE and the unexercised UE.[56,57] If results from this current research can prove that CE is not spatially confined, facilitating neuroplasticity after stroke could occur by exercising any muscle unilaterally and benefiting motor areas as a whole. This thesis will contribute to current literature in the field by administering an acute bilateral and

unilateral leg extension exercise bout whilst examining changes in the unexercised UE to determine the magnitude of neuroplasticity as a result of this intervention.

1.4 Significance

A bilateral strength gain in addition to bilateral changes in corticospinal excitability has already been shown in healthy individuals and individuals with stroke following CE.[17,21,24,26,48,54,65] However, these changes were seen at the level of the homologous muscle. If unilateral resistance exercise had the potential to show widespread benefits beyond the cortical representation of homologous muscles this would suggest further benefits of administration of CE for clinical practice. Further investigating the limits of CE in healthy individuals using TMS will help when implementing neurorehabilitation interventions to patients with stroke in Canada.

2. Acute Lower Extremity Resistance Exercise and the Effects on Corticospinal Excitability in the Unexercised Upper Extremity

2.1 Introduction

In the present study we investigated how an acute LE resistance exercise bout would influence corticospinal excitability in unexercised UE in healthy individuals. Seated leg extensions were chosen as the form of resistance exercise. TMS outcome measures were collected from the unexercised UE [Abductor Pollicis Brevis (APB) muscle]. Leg extension exercises were selected because this exercise targeted a large muscle group in the LE. In addition, the use of leg extension exercises allowed for isolation from the UE and ensured the APB was relaxed during exercise. This is similar to past research that investigated the unexercised UE after leg press exercises.[17,48,57] Abductor pollicus brevis muscle was selected as the muscle to derive TMS outcome measures because it is a targeted muscle for rehabilitation as it is crucial for grasping and other activities of daily living following a stroke.[4,66,67] The current study was conducted over two-days using a within subject study design. There were two conditions: bilateral leg extensions and unilateral leg extensions. Each participant completed both conditions in a random order. Prior to and following resistance exercise, measures of strength [maximal voluntary isometric contraction (MVIC)] and neurophysiology measures were taken. I hypothesized that both bilateral and unilateral exercise would increase strength bilaterally in the LE by means of CE. Further, I predicted that the resistance exercise intervention used here would impact corticospinal excitability. Specifically, I expected to find increased corticospinal excitability (MEP's), decreased intracortical (SICI), corticospinal (CSP) and

interhemispheric (TCI) inhibition and altered measures of spinal excitability (H-reflex and M-wave max) following exercise in the unexercised UE.

2.2 Materials and methods

This present study was approved by University of British Columbia's (UBC) Clinical Research Ethics Board (certificate #H19-00350). All participants independently provided written and verbal informed consent, in accordance with the principles of the Declaration of Helsinki.

2.2.1 Participants

Fourteen healthy individuals were recruited to participate in the current study. Data from two participants were not collected as planned as a result of the research suspension associated with the COVID-19 pandemic. One participant was recruited but never began the study. Another completed day one of the testing but was unable to return for the second timepoint before the research shutdown at UBC. This individual's data were not included in the current dataset. As a result, this thesis contains data from 12 participants rather than the planned 15.

Twelve healthy participants between the ages of 19 and 39 (mean age ± standard deviation (SD): 25.1 ±5.14; 3 males **Table 2-1**) were recruited from UBC and the local community. Participants were included if they showed a MEP during TMS collection and were right-hand/leg dominant individuals. Individuals were excluded if they had a history of any neurological disorder, including, but not limited to dementia, stroke, multiple sclerosis, Parkinson's, traumatic brain injury, psychiatric disorders, and substance abuse. Additionally, they were excluded if they had any contraindications to TMS based on established contraindications including seizures and epilepsy.[68] TMS contraindications were assessed through the Brain Behaviour Lab TMS Screening Questionnaire (**Appendix A**). Exclusion also took place if they were unable to exercise, had a chronic disease, comorbidities or other

contraindications to exercise. Any history of knee injuries such as meniscus tears, or ligament tears that might affect performance also resulted in exclusion. The Physical Activity Readiness Questionnaire Plus (PAR-Q +) and an additional screening form was used to determine these contraindications (Appendix B & C). No one was excluded based on sex, gender, race, religion or ethnicity.

Participant ID	Sex	Age	Mass (kg)	Condition Day 1
CE01	F	20	95	Unilateral
CE02	F	20	61	Bilateral
CE03	F	24	70.5	Unilateral
CE04	F	23	75	Unilateral
CE05	F	23	54.5	Unilateral
CE07	M	32	77	Unilateral
CE08	F	20	64	Bilateral
CE09	M	26	75	Unilateral
CE10	M	23	62	Bilateral
CE11	F	29	58	Unilateral
CE13	F	23	62	Unilateral
CE14	F	36	44.5	Bilateral

Table 2-1. Participant characteristics.
DOB, date of birth; F, female; M, male. CE06 and CE12 were unable to participate in the entirety of the study despite being recruited due to unexpected circumstances (COVID-19).

2.2.2 Informed consent

On both days, participants came to the Brain Behaviour Laboratory on the third floor of UBC Hospital. Prior to signing informed consent, participants were given a thorough explanation of the study and their role. They were provided information on the exercise session, the TMS session as well as the overall design and protocol. It was explained that they could withdraw at any time from the study and information would be kept confidential. Following this, they were required to complete and sign informed consent. Participants were also required to fill out a TMS

screening questionnaire (Brain Behaviour Laboratory Transcranial Magnetic Stimulation Screening Form Version 3, 2012) **Appendix A**. To screen participants for any contraindications to exercise, participants completed the PAR-Q+ from the Canadian Society for Exercise Physiology (Canadian Society for Exercise Physiology, 2002) **Appendix B**. If individuals had any contraindications to either exercise or TMS they were excluded from the study. Lastly, participants completed a final questionnaire specific to this study that addressed previous knee injuries, histories of neurological disorders and substance abuse **Appendix C**. No recruited participants had exclusions to TMS or exercise.

2.2.3 Experimental design

This study was a within-subject repeated measures design. Participants made two, three-hour visits to the Brain Behaviour Laboratory. On day one, participants were provided with informed consent, the PAR-Q+, TMS screening form, and an additional questionnaire specific to this study to determine if participants had a history of knee surgery or current knee pain. Participants then completed a baseline assessment of corticospinal excitability using TMS and peripheral nerve stimulation on APB muscles (**See Neurophysiology sections: 2.2.6 & 2.2.7**). Prior to recruitment, individuals were randomized to complete either the bilateral or unilateral resistance exercise condition on their first visit. Participants completed the other condition on their next visit (day two). Exercise was completed in the Motion Analysis and Biofeedback Laboratory, managed by Dr. Michael Hunt. Immediately following the intervention, individuals returned for a post-exercise assessment in the Brain Behaviour Lab to analyze changes in corticospinal excitability. Visits were separated by a minimum of two weeks to allow for an appropriate wash out period.[69] Total time commitment for participants was 6 hours in the laboratory. **See Figure 2-1.**

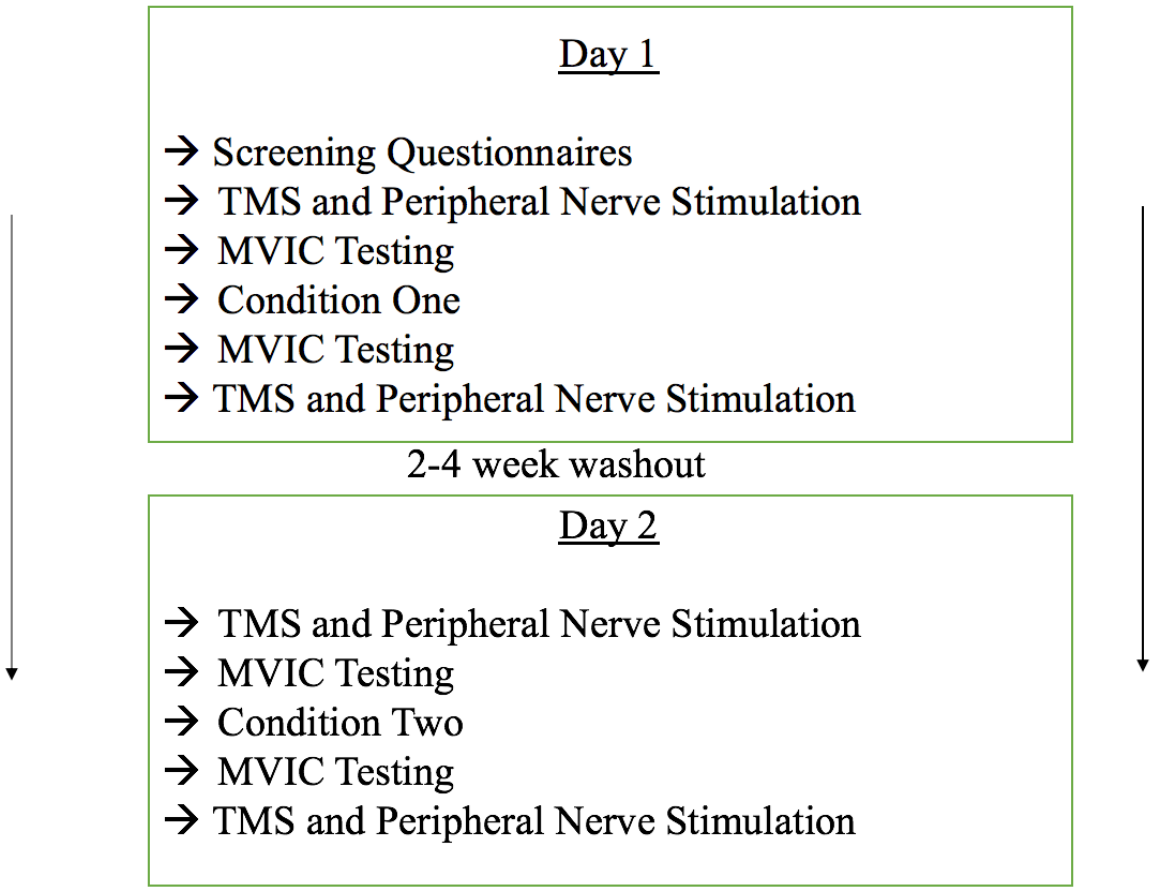

Figure 2-1. Experimental design.

2.2.4 Equipment for study

For resistance exercise and for strength measures in the lower extremity the Biodex System 4 Pro™ and Biodex Advantage Package Software (Biodex Medical Systems Inc, Shirley, NY) was used (**Figure 2.2**). TMS was collected using a Magstim BiStim² and 200² magnetic stimulator, through a 70 mm P/N 9790 figure-of-eight coil (Magstim Co. Ltd., Whitland, Carmarthenshire, UK). For TMS sessions, an electromyography (EMG) was used to collect muscle activity. EMG was also collected during exercise to ensure non exercised limbs remained at rest. For TMS and peripheral nerve stimulation, EMG surface electrodes (1 cm x 1 cm

Kendall™ Ag^{+}/AgCl Foam Electrodes with Conductive Adhesive Hydrogel, Covidien™, Mansfield, MA, USA) were placed on the APB muscle belly bilaterally. EMG surface electrodes were arranged in a bipolar configuration and a ground electrode was placed on the back of the hand. To prepare the skin for the electrodes, individuals had the area cleaned with isopropyl alcohol and skin preparation gel (NūPrep Skin Prep Gel, Weaver and Co., Aurora, CO, USA). EMG was recorded and monitored using 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). A bar electrode (cathode distal; Digitimer Ltd., Welyn Garden City, Hertfordshire, UK) with conducting paste (Ten20® Conductive, Weaver and Co., Aurora, CO, USA) was also placed upon individuals' median nerve, which is located on the interior distal portion of the arm above the wrist. The bar electrode was secured with tape and then connected to a DS7AH HV Constant Current Stimulator (Digitimer Ltd., Welyn Garden City, Hertfordshire, UK). Frequency of peripheral nerve stimulations was set by using LabChart Software. Labchart software was also used to monitor EMG during TMS and peripheral nerve stimulation measures.

Figure 2-2. Participant in Biodex Systems 4 Pro.
Participants is seated and strapped into position in order to restrict movement outside of the leg during maximal voluntary isometric contraction testing and training.

2.2.5 Exercise protocol

Prior to recruitment, participants were randomized to either take part in a bilateral resistance exercise bout or unilateral resistance exercise bout on day one. Resistance exercise in this study was leg extensions where LE extensor muscles were contracting while extending against external resistance from the Biodex. This acute bout of resistance exercise was conducted in the lab. On day two, participants engaged in the whichever exercise condition that was not performed on day one. Prior to the resistance exercise, individuals had baseline corticospinal excitability measures taken **(See neurophysiology sections: Section 2.2.6 and 2.2.7)**. MVIC on each leg was also performed prior to exercise. Exercise took place in the Motion Analysis and Biofeedback Laboratory, located across the hall from the Brain Behaviour Laboratory, also in

UBC Hospital. The Motion Analysis and Biofeedback Laboratory contains the Biodex System 4 Pro™ where exercise was conducted and MVIC was assessed.

Participants sat in the Biodex machine. The chair was adjusted to fit the participant by adjusting the height and distance from the dynamometer. The seat position was recorded to ensure chair adjustments were consistent across days. Once the participant was positioned for exercise, they were strapped into the chair to isolate movement beyond that of the legs. Prior to exercise, participants performed two isometric knee extensions on each leg against a perpendicular force at 60º to calculate a MVIC from the Biodex. Isometric contractions were maintained for 5 seconds. Each resistance exercise group had two attempts separated by a one-minute rest on each leg and their larger attempt was accepted as their maximal contraction. For this thesis, strength was operationalized in torque and was measured in newton meters per kilogram (Nm/kg). An increase in strength is indexed by an increase in torque.

Seventy percent of MVIC was used as the minimum exercise intensity. Previous CE studies suggest the magnitude of M1 excitability and inhibition is enhanced with contractions at a higher percentage of the individual's maximum.[59,60] Prior to exercise, two electrodes were placed on participants' rectus femoris muscle belly and a ground electrode was placed on the participants' patella bilaterally to monitor leg extensor muscle activity. Existing electrodes from corticospinal excitability measures remained situated on the APB muscle belly bilaterally during exercise. This allowed monitoring of activity within both APB and the quadriceps muscles during exercise to ensure unexercised muscles remained relaxed. EMG of the resting arms and legs were recorded using LabChart Software (LabChart 7.0, AD Instruments Inc., Colorado Springs, CO) to ensure the least amount of muscle activity was present. Using the Biodex, knee extensions were performed at 70% of MVIC during warm up and exercise either unilaterally or

bilaterally depending on condition while the arms remained relaxed. A warmup was provided which consisted of 3 sets of 5 repetitions. Exercise consisted of 5 sets of 10 repetitions. Although there is currently no set optimal dose of resistance exercise for CE studies, this exercise dose was selected based on a recent meta-analysis examining the impact of training loads on contralateral limbs after unilateral exercise. It concluded the optimal exercise dose was 3-5 sets with 8-15 repetitions in order to see the most contralateral transfer.[70] The intensity of CE is optimal when the trained side is the individual's dominant side.[71] For this reason, only right-leg dominant participants were recruited so all unilateral exercise was performed on the right leg. During exercise, participants were provided with feedback on performance by a pink line on the Biodex that indicated 70% of their MVIC. Participants were able to modulate force production during exercise to ensure they were achieving at least 70% of their maximal contraction with each leg extension. During exercise, they were instructed to keep their arms and non-exercised leg (if applicable) as relaxed as possible. During the bilateral exercise condition, EMG was also used to monitor activity in both legs to ensure that each leg was working equally. After exercise, participants received a 1-minute break before performing two more MVIC's on each leg. During MVIC's and exercise participants were verbally encouraged to motivate them.

Following this, participants immediately returned to the Brain Behaviour Laboratory to complete post exercise measures of corticospinal excitability.

2.2.6 TMS measures

TMS was measured in all 12 participants. Electrodes were placed on both APB muscle belly's as described above (**See Equipment for study: Section 2.2.4**). When TMS was triggered, data was collected as EMG using Labchart Software. Participants were instructed to stay awake with their eyes open and stay as relaxed as possible during collections.

TMS was delivered by the Magstim BiStim^2 and 200^2 magnetic stimulators, through a 70 mm P/N 9790 figure-of-eight coil (Magstim Co. Ltd., Whitland, Carmarthenshire, UK). Prior to each collection, participant localization and coil calibration were conducted to confirm location and trajectory of the TMS coil using the Brainsight™ neuronavigation system (Rogue Research Inc., Montreal, QC, Canada). During TMS stimulation, EMG amplitude was monitored on LabChart (LabChart 7.0, AD Instruments Inc., Colorado Springs, CO). The TMS coil was held over the scalp at a 45º angle to the midsagittal plane over M1 to generate a magnetic pulse in the posterior-anterior direction, perpendicular to the precentral gyrus.[72] During each baseline assessment on both days **(See Exercise protocol: Section 2.2.4)** participants' 'hot spot', was found by positioning the TMS coil over M1 to a spot that elicited the greatest and most consistent MEP in the contralateral APB. Once found, it was marked digitally on Brainsight™ and used as the focal point for TMS delivery. After finding APB representation, resting motor threshold (RMT), the lowest stimulator output that can elicit a MEP at 50 μv peak to peak amplitude in the relaxed muscle in 5/10 consecutive TMS stimuli was determined.[44] This was found in both hemispheres and collected during the baseline assessments on day 1 and day 2 **(See Table 2-2)**.

Ten stimulations per hemisphere per TMS measure were delivered. Individuals' received stimuli in a randomized order to prevent anticipation effects.[73] All TMS measures were delivered in both hemispheres during baseline and post-exercise on each day. Data was recorded using LabChart software and EMG data was later analyzed offline with custom MATLAB scripts. Day two TMS measures and collection were identical to day one.

Single-Pulse: Motor Evoked Potentials (MEPs). MEPs can be used to quantify corticospinal excitability. The amplitude of the MEP can provide information on how excitable

the corticospinal neurons are. Once RMT was established, 10 MEPs were collected with TMS intensity set to 130% of RMT.[48,74] This measure was conducted during baseline and post-exercise on both days.

Paired-Pulse: Short-Interval Intracortical Inhibition (SICI). SICI characterizes inhibitory interneurons. SICI followed paired-pulse protocols.[40] SICI requires a conditioning stimulus followed by a suprathreshold test stimulus to cause a depression in the MEP when the pulses are separated by 1-6ms.[75]A subthreshold conditioning stimulus (CS) of 80% RMT was followed by a suprathreshold test stimulus (TS) at 1mV over APB representation on M1 with an interstimulus interval (ISI) of 2.5ms.[40,76] First, 10 TS pulses were collected alone with an amplitude of ~1mV. After this, 10 paired pulses of CS+TS were collected. A new TS was established for each hemisphere for baseline and post-exercise. This measure was performed bilaterally.

Single- Pulse: Contralateral Silent Period (CSP) and Ipsilateral Silent Period (iSP). CSP and iSP provide measures of corticospinal inhibition and transcallosal inhibition (TCI) respectively during a sustained contraction of the muscle of interest (APB).[77] For both measures (CSP and iSP) participants were instructed to squeeze a dynamometer for 5 seconds to activate APB and determine maximal voluntary contraction (MVC). Following this, during TMS stimulations participants were instructed to maintain 50% and 20% of their MVC for iSP and CSP, respectively.[78] Force output was shown to participants on LabChart dynamometer software so they could modulate their contraction to ensure contractions were consistent throughout each measure. Participants were instructed to maintain the contraction during pulses and the non-active arm was instructed to remain relaxed. Ten TMS pulses for each measure were delivered at 130% and 150% RMT to measure CSP and iSP, respectively. For CSP measures, the TMS coil was placed contralaterally to the active APB, for TCI the TMS coil was placed ipsilaterally to the

active APB. Data collectors constantly monitored surface EMG activity in the resting and active APB through Labchart software. If participants were unable to maintain the percentage of MVC contraction required due to fatigue, TMS pulses were stopped until participants' regained contraction. These measures were performed bilaterally.

2.2.7 Peripheral nerve stimulation measures

To determine spinal excitability, peripheral nerve stimulation was used to measure participants' H-reflex. A bar electrode was placed on the median nerve, on the inside, lower portion of the arm proximal to the wrist. The location on the median nerve where the bar electrode was placed was outlined with a pen on the participants' arm to ensure that it was placed in the same position post-exercise. The electrodes were placed on APB, two on the muscle belly and one on the back of the hand. H-reflex is induced electrically from a bar electrode and displays a monosynaptic reflex when participants are contracting.[79,80] In this study, a maximal motor-wave or M_{max} was found prior to H-reflex. M_{max} is a motor response that represents maximal recruitment of alpha motoneurons (α-MNs).[80] This was found by slowly increasing electrical nerve stimulation intensity on the Digitimer/ stimulator until a plateau was found on the EMG, indicating the maximal recruitment of α-MNs. Once M_{max} was found, participants performed a 5-second MVC that activated the APB muscle using a dynamometer attached to Labchart dynamometer software. Force output was then shown to participants on LabChart dynamometer software so they were able to modulate their force to maintain a contraction of 10% of their MVC during the collection of H-reflex. Stimulation intensity was set so that the M-wave corresponded to 20% of the M_{max} to keep stimulation intensity consistent across participants. A minimum of 40 sweeps of H-reflex were then recorded while participants sustained a 10% MVC contraction. This was performed bilaterally at baseline and post exercise.

2.2.8 Data processing

All measures of strength were operationalized as torque (Nm/kg). An increase in torque represented an increase in strength. Torque was normalized to each participants' mass in kilograms (Nm/kg).

All TMS measures and peripheral nerve stimulation measures were extracted from EMG data from APB muscle. MEPs were processed using a custom MATLAB script (Mathworks Natwick, MA). MEPs at 130% RMT was processed by quantifying peak to peak amplitudes of MEPs. SICI was analyzed as a ratio of paired stimulations (TS and the CS) with larger values indicating less inhibition. CSP and iSP were processed on a fully rectified EMG for each participant. The onset of the CSP was the onset of the MEP (when the EMG is five times greater than the pre-stimulus mean EMG). Mean pre-stimulus EMG was the muscle activity 100ms prior to the stimulation. The onset of the iSP is defined as the post-stimulus time where the rectified EMG signal dropped below pre-stimulus EMG muscle activity. When the EMG signal returns to the pre-stimulus mean EMG this is defined as the CSP and iSP offset. The full silent period was defined as the duration between onset and offset. Longer duration silent periods mean greater inhibition. TCI was also analyzed through iSP mean as a ratio of the Prestim Mean EMG/ iSP mean. The larger the iSP mean, the less inhibition.

Peak to peak amplitudes of m-waves and H-reflexes were computed offline from an unrectified EMG. M-waves and H-reflex were processed by quantifying peak to peak amplitudes on the EMG. H-reflex was normalized to the individual participants EMG and M_{max}. H-reflex amplitude was expressed as a ratio of the H-reflex amplitude (mV) relative to the m-wave amplitude (mV). The m-wave amplitude reflected 20% of participant's individualized M_{max} to

ensure consistency across participants. Larger values indicated a larger H-reflex and increased spinal excitability.

Custom MATLAB scripts (Mathworks, Natick, MA) were used to quantify MEP, SP, m-wave, and H-reflex.

2.2.9 Statistical analysis

All statistical tests were performed using SPSS statistics 25.0 (IBM Corporation, Armonk, NY, USA). Significance threshold was set at $p \leq 0.05$. Descriptive statistics were expressed as means ± standard deviations. Prior to parametric statistical tests, assumptions of sphericity, normality, and heterogeneity of variances were evaluated using appropriate statistical tests. For the tests, T0= Baseline and T1= Post exercise. For all TMS measures in the unilateral condition, the right leg was exercised and for that reason the exercised hemisphere is the left hemisphere, and the unexercised hemisphere is the right hemisphere

2.2.9.1 Within-subject baseline comparisons

To confirm baseline measures were not significantly different prior to further analyses being conducted (**See Table 2-1)** paired-samples T-tests were conducted for all measures (**See Exercise protocol and TMS measures: 2.2.5 & 2.2.6**). If $p > 0.05$, the average of the means from baseline for each condition were used as T0.

2.2.9.2 Strength based dependent measures

To detect changes in strength (MVIC) between baseline and post-exercise in each leg a within subject two-way repeated measures (rm) Analysis of Variance (ANOVA) was performed for both the bilateral (n=12) and unilateral (n=12) condition. Strength was measured in torque, that was quantified in newton meters (Nm/kg). The within subject factors were LEG (Right, Left) x TIME (T0, T1). Following this, a three-way (TIME: T0, T1 X LEG: right, left X

CONDITION: bilateral, unilateral) rmANOVA was performed to analyze mean differences in improvements in MVIC between the conditions.

2.2.9.3 TMS based dependent measures

To examine change in corticospinal excitability across time, separate two-way rmANOVA were conducted using MEP at 130% RMT as a dependent measure for the bilateral (*n*=12) and unilateral (*n*=12) condition. Corticospinal excitability was measured in amplitude (mV) of the MEPs. The within-subject factors were HEMISPHERE (Left, Right) x TIME (T0, T1).

Contralateral silent period was examined to detect changes in corticospinal inhibition between time points. CSP was measured in duration of the silent period in milliseconds (ms) where a shorter duration indicated less inhibition. Separate two-way rmANOVA HEMISPHERE (Right and Left) x TIME (T0 and T1) were performed separately for the bilateral (*n*=11) and unilateral (*n*=12) conditions.

Transcallosal inhibition was used to detect changes in interhemispheric inhibition between time points. TCI was measured in iSP duration, where a shorter duration (ms) of the silent period indicates less inhibition and also measured by iSP mean, where a larger iSP mean indicates less inhibition. One participant did not have a baseline measure for TCI for one of the testing days; after confirming there was no difference in other participants' baseline TCI between days, this participant's baseline measure from day one was used for day two. Separate two-way rmANOVA TIME (T0, T1) X HEMISPHERE (Right, Left) were performed for the bilateral (*n*=12) and unilateral (*n*=12) conditions for iSP duration and iSP mean.

Short interval intracortical inhibition was examined to detect differences in intracortical inhibition in hemispheres between time points. SICI is expressed as a ratio of the unconditioned

TS to the CS as a percentage of inhibition where a larger percentage indicates less inhibition. A two-way rmANOVA Time (T0, T1) X HEMISPHERE (Right, Left) was conducted separately for the bilateral (*n*=12) and unilateral (*n*=11) condition.

2.2.9.4 Peripheral nerve stimulation based dependent measures

Motor wave max was studied as an index of maximal α-MN recruitment so that H-reflex could be normalized to individuals' m-wave amplitude. M_{max} was quantified through the peak to peak amplitude (mV) of the m-waves during maximal stimulator output. The largest M-wave was accepted as the participants M_{max}. A two-way rmANOVA APB (Right, Left) x TIME (T0, T1) was performed separately for the bilateral (*n*=12) and unilateral (*n*=12) condition. Participant CE05 was missing M_{max} values on their second day of participation in the bilateral condition. A paired-samples T-test showed no difference between baseline across days for other participants so CE05's baseline M_{max} from day 1 was used as their baseline M_{max} for day 2. CE05's post M_{max} was imputed with the post-exercise M_{max} of another participant who had similar demographics and M_{max} values across days.

The H-reflex was examined to consider changes at the level of the spinal cord by quantifying the response of the monosynaptic reflex when the median nerve was electrically stimulated. H-reflex amplitude was expressed as a ratio of the H-reflex amplitude (mV) relative to the m-wave amplitude (mV). The m-wave amplitude reflected 20% of participant's individualized M_{max} to ensure consistency across participants. A two-way rmANOVA was conducted separately for each the bilateral (*n*=8) and unilateral (*n*=8) condition. The within-subject factors were APB (Right, Left) x TIME (T0, T1). Not all participants were able to elicit an H-reflex or sustain an H-reflex for enough trials to justify extracting values so for that reason the sample size is *n*=8.

2.2.9.5 Measures of effect sizes

This study was underpowered because of a smaller than intended sample size due to the COVID-19 pandemic. Cohen *d*'s effect sizes (ES) (small ≤ 0.5; moderate 0.51-0.79; and large ≥ 0.80)[81] were used to determine the magnitude of the intervention on neurophysiology measures that trended towards significance but did not meet alpha level. This was done using the Cohen's *d* formula:

$$Cohen's\ d = \frac{\text{Mean 1} - \text{Mean 2}}{\text{Standard deviation pooled}}$$

Effect sizes were also calculated to achieve another measure of the magnitude of the resistance exercise intervention on strength.[81,82] Specifically, for strength training research, ES accounts for variability of strength improvements within the sample, rather than relying on *p*-values or the average percentage increases in strength. To calculate ES of strength:

$$Pre - Post\ ES = \frac{\text{Posttest mean} - \text{Pretest mean}}{\text{Pretest standard deviation}}$$

Here, the difference between the two means is divided by the variation of the pretest mean. Rhea suggested that when investigating the magnitude of change in strength, the scale proposed by Cohen (1969) may not be best in strength training research. To characterize the magnitude of ES after a resistance exercise intervention the 'Scale for determining the magnitude of ES in strength training research' was used. Using this scale (trivial, <0.5; small 0.5-1.25; moderate, 1.25-1.9; large >2.0) ES were used to determine the magnitude of change in MVIC at baseline compared to post-exercise. [82]

Effect sizes were only reported for measures that trended towards alpha level but did not reach significance.

2.3 Results

Complete results are shown in **Table 2-3**.

2.3.1 Baseline measures

Paired-Samples T-tests were conducted to compare baseline MVIC, and neurophysiology measures across days. There was no difference between the means of baseline values, $p > 0.05$.

See Table 2-2.

			Time-Point Mean (SD)		
Measure	Hemisphere/ side	*n*	Bilateral	Unilateral	p-value
MVIC (Torque, Nm/kg)	Right Leg	12	2.41 (0.325)	2.52 (0.515)	0.281
	Left Leg	12	2.41 (0.492)	2.45 (0.541)	0.629
RMT (%MSO)	LH	12	49.3 (8.85)	48.6 (8.40)	0.191
	RH	12	51.7 (9.04)	50.7 (10.78)	0.493
130% RMT (mV)	LH	12	1.61 (0.898)	1.94 (1.261)	0.196
	RH	12	1.20 (0.600)	1.17 (0.783)	0.866
SICI TS (~1mV)	LH	12	1.18 (0.277)	1.26 (0.361)	0.509
	RH	12	1.13 (0.260)	1.11 (0.311)	0.774
SICI (% of TS)	LH	12	17.7% (10.9)	28.2% (23.4)	0.128
	RH	12	23.9% (24.4)	21.1% (23.7)	0.620
CSP (s)	LH	12	0.169 (0.0225)	0.171 (0.0258)	0.689
	RH	12	0.174 (0.0350)	0.176 (0.0314)	0.713
iSP duration (s)	LH	12	0.0445 (0.01138)	0.0421 (0.00823)	0.414
	RH	12	0.0420 (0.0153)	0.0404 (0.0102)	0.703
iSP-Mean (% Prestim mean EMG)	LH	12	0.594 (0.0880)	0.572 (0.0971)	0.462
	RH	12	0.555 (0.0693)	0.567 (0.0793)	0.608
Mmax (mV)	Right APB	12	14.8 (4.97)	15.4 (6.13)	0.537
	Left APB	12	12.3 (3.99)	13.8 (4.69)	0.063
H-reflex (% of m-wave)	Right APB	8	36.5% (9.83)	41.3% (18.43)	0.555
	Left APB	8	40.3% (21.7)	33.8% (18.5)	0.332

Table 2-2. Baseline measures
p-values from paired-samples t-tests. There was no difference between baseline measures in participants across days ($p>0.05$). *n* is sample size. SD is standard deviation. APB, abductor pollicus brevis; LH, left hemisphere; RH, right hemisphere; MVIC, maximal voluntary isometric contraction; MEP, motor-evoked potential; mV, millivolt; SICI, short interval intracortical inhibition; TS, test stimulus; CSP, contralateral silent period; iSP, ipsilateral silent period; EMG, electromyography; M_{max}, motor-wave max; H-reflex, Hoffmans reflex.

2.3.2 Aim 1: Changes in strength

A two-way (Time X Leg) rmANOVA with MVIC as the dependent measure for the bilateral condition indicated a significant main effect of time that showed increase in strength (Nm/kg) in both legs after resistance exercise (F= 5.288, p=0.042). There was no main effect of leg, so no differences between the legs in the increase in strength (Nm/kg) after exercise (F=0.021, p=0.888). The right leg had a 4.8% increase in strength and the left leg a 4.3% increase in strength.

A two-way (Time X Leg) rmANOVA with MVIC as the dependent measure for the unilateral condition showed a significant main effect of time (F=12.0.96, p=0.005). There was a strength increase in both legs in the unilateral condition, even though only the right leg was exercised. There was no main effect of leg indicating no difference between the legs in how much they increased in strength (F=1.567, p=0.237). For the unilateral condition, the right/exercised leg had an average of a 7.7% increase in strength and the left leg/unexercised leg had a 7.7% increase in strength.

Following these analyses, a three-way (Time X Leg X Condition) rmANOVA was performed to detect differences in the increase in strength between conditions. There was a significant main effect of time (F=22.799, p<0.001), no main effect of leg (F=0.778, p=0.396), and no main effect of condition (F=2.263, p=0.169). **See Figure 2-3**.

These data suggest that there was an overall increase in leg extension strength in both conditions and that strength in the unexercised leg increased with exercise in the unilateral condition. There was no main effect of leg in both conditions, showing a similar increase in strength between legs. No significant main effect was shown between conditions showing that

increases in strength were similar whether participants exercised unilaterally or bilaterally. Individual MVIC values are shown in **Figure 2-4**.

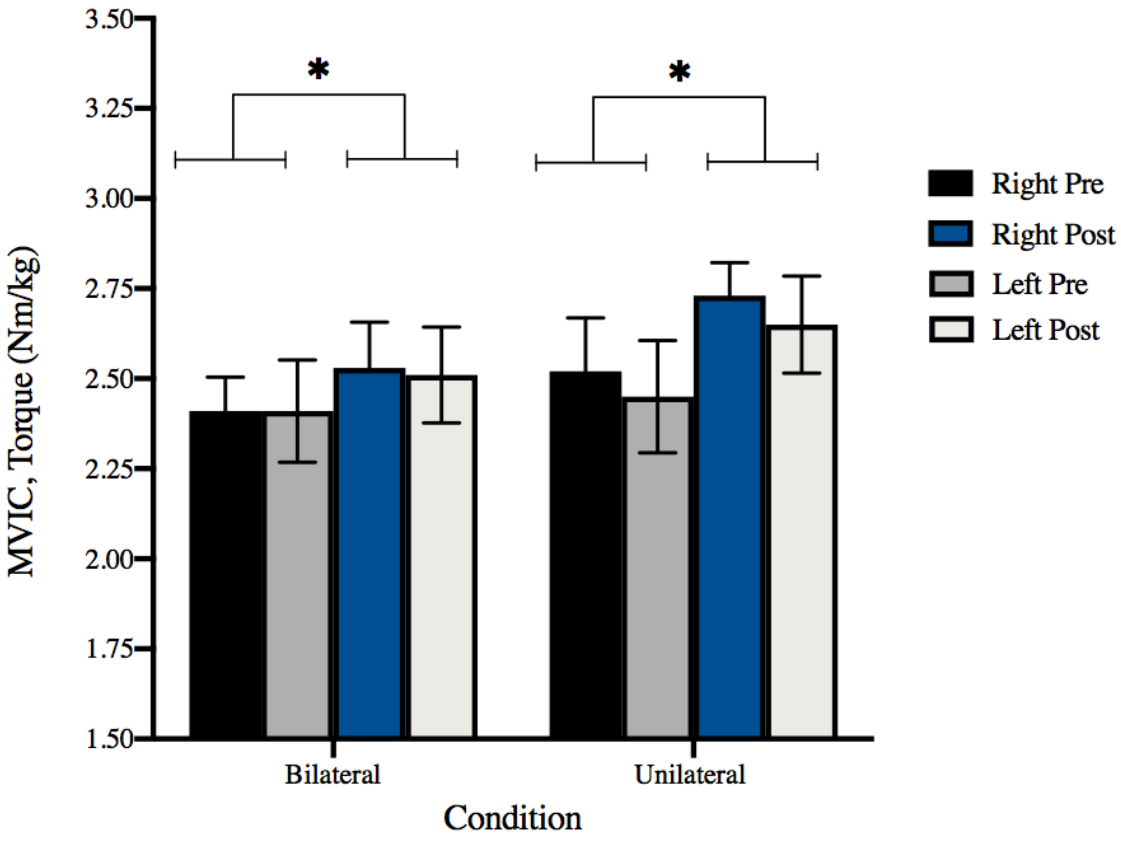

Figure 2-3. Bilateral and unilateral leg extension exercise increase strength bilaterally. For the unilateral condition the right leg is the exercised leg. Black Bars indicate the right leg at baseline (T0) and the blue bars represent the left leg at baseline (T0). The light grey bars indicate the right leg post-exercise (T1) and the white bars indicate the left leg post-exercise (T1). The Y-axis measures strength in torque (Nm/kg). Higher bars indicate an increase in strength. MVIC is significantly increased with exercise in both legs and both conditions (*n=12*). Proportion of increase in strength was not affected by the condition or the leg. Data is presented in mean ± SE. * donates statistical significance ($p \leq 0.05$).

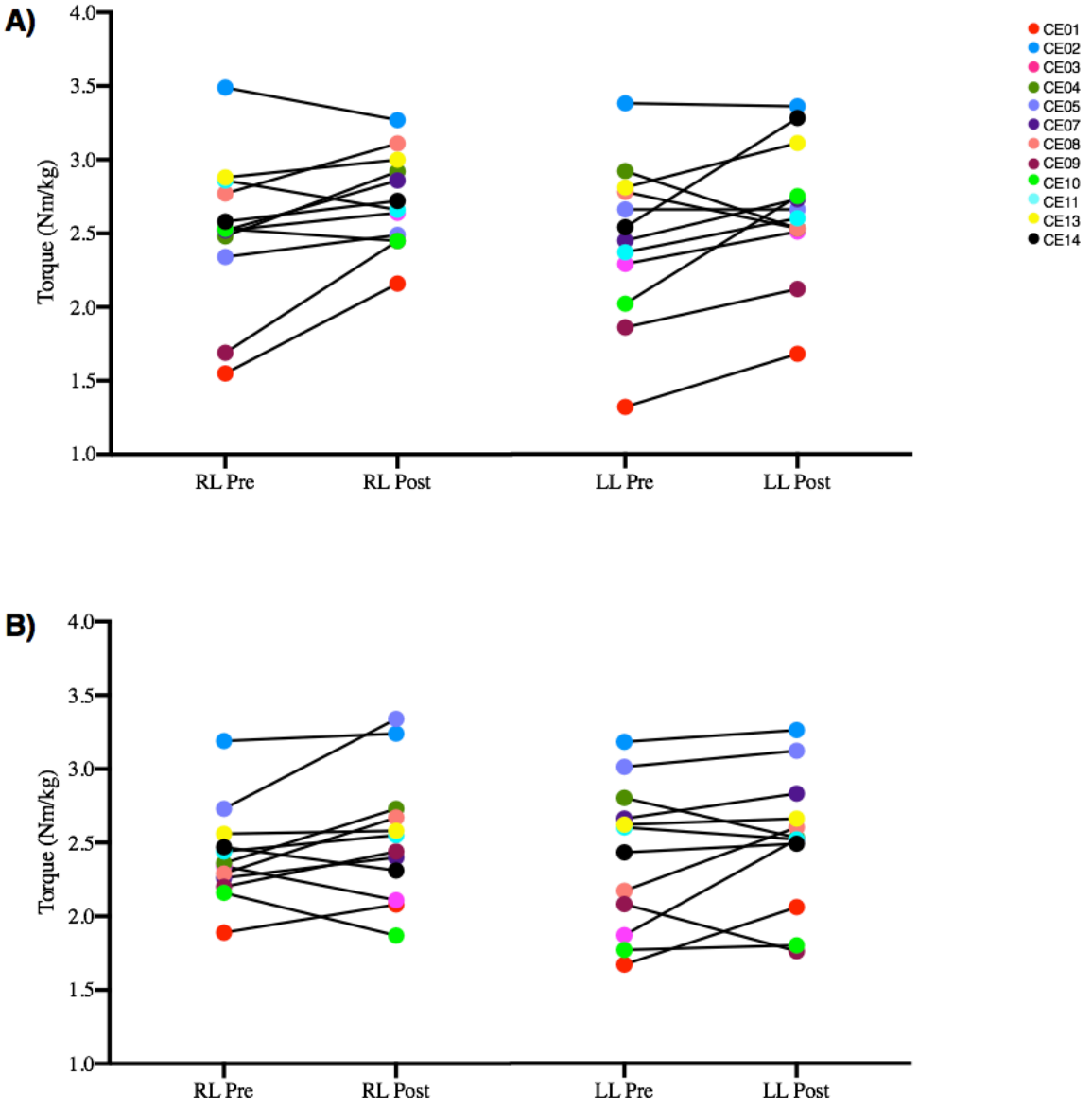

Figure 2-4. Individual MVIC values for both conditions.
n=12. Each point donates the MVIC of an individual participant. Each colour represents a different participant. RL, right leg; LL, left leg. Higher points indicate an increase in strength. A) The unilateral condition, the RL is the exercised leg and the LL is the unexercised. B) The bilateral condition * donates statistical significance ($p \leq 0.05$).

2.3.3 Aim 2: Changes in corticospinal excitability in the bilateral condition

2.3.3.1 TMS measures

A two-way (Time X Hemisphere) rmANOVA was run to assess the impact of bilateral leg extension exercise on MEP amplitude at 130% RMT. Resistance exercise did not impact MEP amplitude as shown by the absence of a main effect of hemisphere and the absence of a main effect of time.

A two-way (Time X Hemisphere) rmANOVA was run to assess the impact of bilateral leg extension exercise on the CSP duration. Resistance exercise did not impact the CSP duration and this was shown by no main effect of time (F=2.083, p=0.180) and no main effect of hemisphere (F=0.275, p=0.611). The data is trending towards a shorter silent period post-exercise in both hemispheres compared to baseline, but this was not significant and only small effect sizes were detected (LH, d=0.32; RH, d=0.23). **See Figure 2-5**

A two-way (Time X Hemisphere) rmANOVA was conducted to assess the effect of bilateral leg extension exercise on TCI as measured through iSP duration and iSP mean. Although there was a trend towards a bilateral decrease in the iSP duration this was not significant as shown through the absence of a main effect of time (F=3.290, p=0.097). Moderate (LH, d=0.51) and large (RH, d=0.99) effect sizes were detected post-exercise, however. There was no main effect of hemisphere (F=2.264, p=0.617). **See Figure 2-6**. The bilateral resistance exercise also had no effect of the iSP mean shown by an absence of a main effect of time (F=0.235, p=0.637) and no main effect of hemisphere (F=3.341, p=0.095).

A two-way (Time X Hemisphere) rmANOVA was conducted to assess the impact of bilateral leg extension exercise on SICI. The resistance exercise decreased inhibition as measured by SICI with a significant main effect of time (F=4.814, p=0.05). This indicated a

release of intracortical inhibition at T1 compared to T0 in both hemispheres as a result of the bilateral resistance exercise. There was no main effect of hemisphere (F=0.425, p=0.528). **See Figure 2-7.**

2.3.3.2 Peripheral nerve stimulation measures

A two-way (Time x APB) rmANOVA was performed to assess the effect of bilateral leg extensions on M_{max}. Resistance exercise had no effect on α-MN recruitment as shown through the absence of a main effect of time (F=0.001, p= 0.977). There was no main effect of APB (F=4.003, p=0.071). **See Figure 2-8**.

A two-way (Time x APB) rmANOVA was performed to assess the effect of bilateral leg extension exercise on spinal excitability in APB as measured through H-reflex amplitude. Spinal excitability in APB was not affected by bilateral leg extensions, this was shown through no main effect of time (F=1.139, p=0.321) or APB (F=0.525, p=0.492).

2.3.4 Aim 3: Corticospinal excitability changes in the unilateral condition

2.3.4.1 TMS measures

A two-way (Time X Hemisphere) rmANOVA was run to assess the impact of unilateral leg extension exercise on MEP amplitude at 130% RMT. Resistance exercise did not impact MEP amplitude as shown by the absence of a main effect of hemisphere and the absence of a main effect of time.

A two-way (Time X Hemisphere) rmANOVA was run to assess the impact of unilateral leg extension exercise on the CSP duration. The resistance exercise did not affect CSP duration in either hemisphere after unilateral leg extension exercise as there was no main effect of time (F= 0.557, p=0.471) or hemisphere (F=0.142, p=0.713). **See Figure 2-5.**

A two-way (Time x Hemisphere) rmANOVA was used to assess the effect of unilateral leg extension exercise on TCI as measured through iSP duration and iSP mean. Unilateral strength exercise in the legs had no effect of iSP duration as shown through no main effect of time (F=1.361, p=0.268). The right/unexercised hemisphere was trending towards a decrease in iSP duration after exercise (d=0.37) and this was not present in the left/exercised hemisphere but there was no main effect of hemisphere (F=1.480, p=0.249) and no interactions present (F=0.894, p=0.365). **See Figure 2-6**. A two-way (Time x Hemisphere) rmANOVA also detected no main effect of time (F=0.017, p=0.899) or hemisphere (F=0.029, p=0.867) in iSP mean after unilateral resistance exercise.

A two-way (Time X Hemisphere) rmANOVA was used to assess the impact of unilateral leg extensions exercise on SICI. Unilateral resistance exercise did not impact SICI as shown through no main effect of time (F=0.063, p=0.807). There was also no main effect of hemisphere (F=0.011, p=0.918), however there was a non-significant trend towards a mean decrease in SICI in the right/unexercised hemisphere (d= 0.22) and an increase in inhibition in the left/ exercised hemisphere (d=0.24) but no interactions were present (F=1.487, p=0.251). **See Figure 2-7**.

2.3.4.2 Peripheral nerve stimulation measures

A two-way (Time x APB) rmANOVA was run to assess the impact of unilateral leg extension exercise on M_{max}. Unilateral resistance exercise decreased α-MN recruitment on both APB's as shown through a significant main effect of time (F= 6.134, p=0.031) with the decrease in M_{max} amplitude. There was no main effect of hemisphere (F=0.170, p=0.688) or interactions present. **See Figure 2-8**.

A two-way (Time x APB) rmANOVA was performed to assess the impact of unilateral leg extension exercise on spinal excitability as measured through H-reflex. Resistance exercise

unilaterally did not impact H-reflex amplitude as shown through the absence of a main effect of time (F= 0.365, p=0.565) and no main effect of hemisphere (F= 0.140, p=0.719).

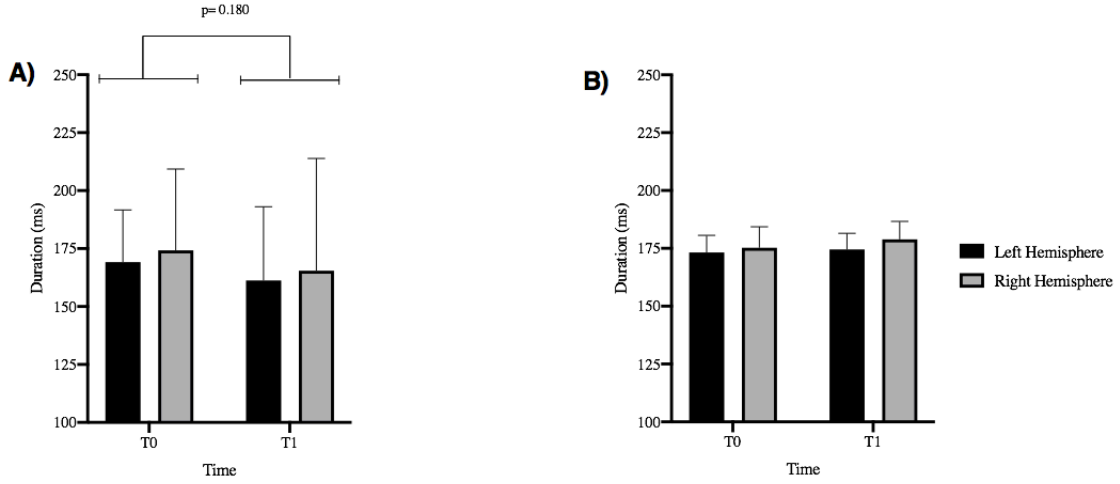

Figure 2-5. Contralateral silent period in both conditions.
Black bars represent the left hemisphere and the light grey bars represent the right hemisphere. T0 is baseline and T1 is post-exercise. Duration is measured in milliseconds (ms). Lower bars indicate a release or decrease in corticospinal inhibition. Although there was no main effect of time or hemisphere in either condition, there was a non-significant decrease in the CSP in both hemispheres for the bilateral condition. A) The bilateral condition (*n=11*). B) The unilateral condition (*n=12*). Data are presented in mean ± SE.

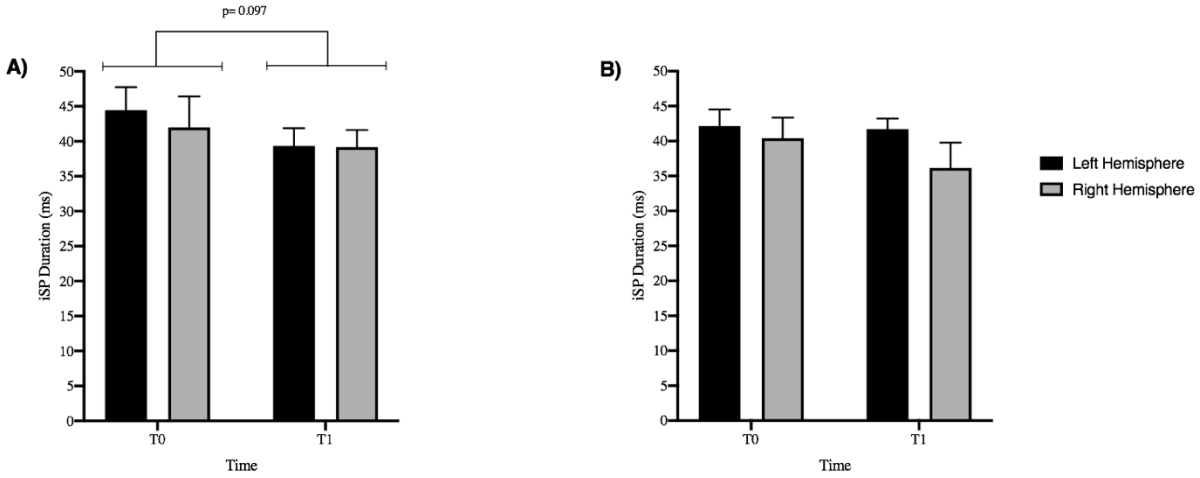

Figure 2-6. Transcallosal inhibition shown in ipsilateral silent period duration (ms) in both conditions.
Black bars are the left hemisphere and grey bars are the right hemisphere. T0 is baseline and T1 is post-exercise. iSP duration is measured in milliseconds (ms). Lower bars indicate a release of inhibition from the contralateral hemisphere to the ipsilateral hemisphere, indicated with a shorter/quicker SP. A) The bilateral condition there is a non-significant decrease in interhemispheric inhibition across time points (*n*=12) B) The unilateral condition shows a non-significant decrease in the right (unexercised) hemisphere (*n*=12). Data are in mean ± SE.

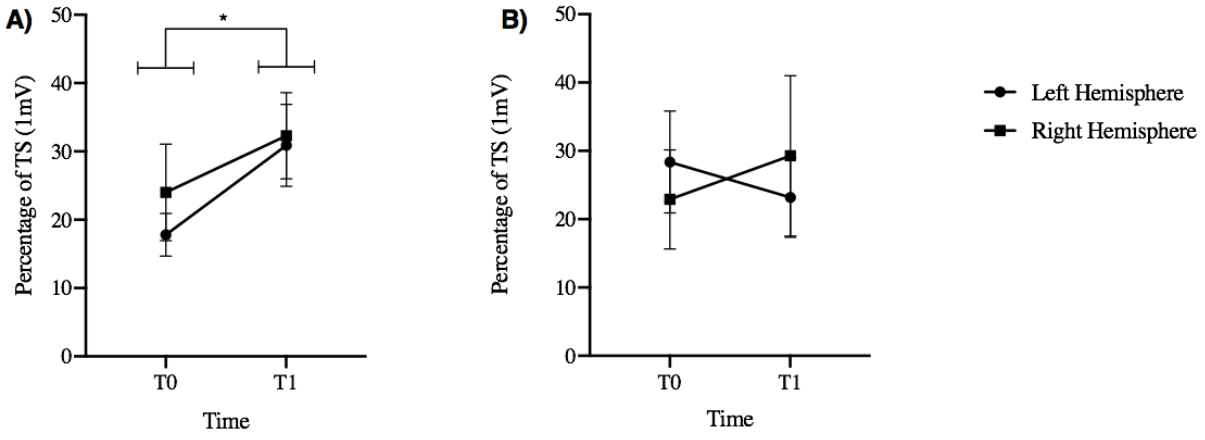

Figure 2-7. Short interval intracortical inhibition in both conditions.
Left Hemisphere is black circle and the right hemisphere is a black square. T0 is baseline and T1 is post-exercise. Y-axis is in percentage of the conditioned stimulus relative to the test stimulus (TS) where higher values indicate less inhibition. A) The bilateral condition (*n*=12) shows a main effect of time, decrease in intracortical inhibition bilaterally post-exercise. B) The unilateral condition (*n*=11). Data are presented in mean ± SE. * donates statistical significance $p \leq 0.05$.

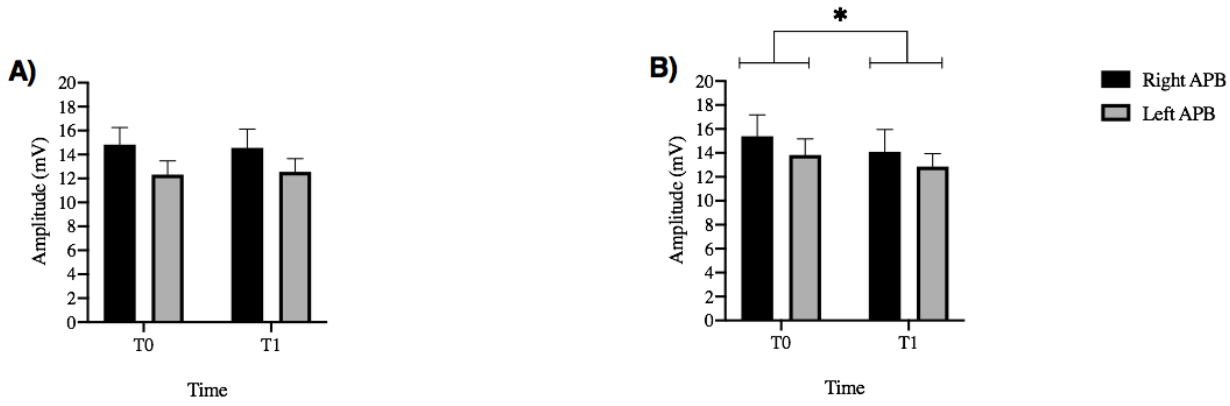

Figure 2-8. M_{max} in both conditions.
Black bars are the right APB muscle and the grey bars are the left APB muscle. T0 is baseline and T1 is post-exercise. Y-axis is in amplitude (mV). APB is abductor pollicus brevis. Lower bars indicate a smaller M_{max}. A) Bilateral condition shows no main effect of time or hemisphere (*n*=12). B) Unilateral condition shows a main effect of time with a bilateral decrease in M_{max} amplitude post-exercise (*n*=12). Data is presented in mean ± SE.* donates statistical significance $p \leq 0.05$.

Table 2-2. Complete results

			Time Point Mean (SD)			Time Point Mean (SD)		
Measure	**Condition**	***n***	**Right Side Pre**	**Right side Post**	**ES**	**Left Leg Pre**	**Left Leg Post**	**ES**
MVIC (Torque, Nm/kg)	Bilateral Unilateral	12 12	2.41 (0.325) 2.52 (0.515)	2.53 (0.438)* 2.73 (0.318)*	0.37 0.41	2.41 (0.492) 2.45 (0.514)	2.51 (0.461)* 2.65 (0.467)*	0.20 0.39
			LH Pre	**LH Post**		**RH Pre**	**RH Post**	
MEP at 130% RMT (mV)	Bilateral Unilateral	12 12	1.61 (0.89) 1.94 (1.26)	1.48 (1.02) 1.70 (0.94)	0.14 0.22	1.17 (0.78) 1.2 (0.60)	1.11 (0.45) 1.31 (0.65)	0.1 0.18
SICI (% of TS)	Bilateral Unilateral	12 11	17.7 (10.9) 28.4 (24.7)	30.9 (20.5)* 23.2 (19.3)	0.84 0.24	23.8 (24.3) 22.5 (24.0)	32.4 (21.7)* 29.3 (38.9)	0.37 0.22
CSP (s)	Bilateral Unilateral	11 12	0.169 (0.02) 0.173 (0.03)	0.161 (0.03) 0.174 (0.02)	0.32 0.04	0.174 (0.03) 0.175 (0.03)	0.165 (0.05) 0.179 (0.03)	0.23 0.13
iSP duration (ms)	Bilateral Unilateral	12 12	44.45 (11.4) 42.13 (8.2)	39.33 (8.8) 41.71 (5.1)	0.51 0.06	42.0 (15.3) 40.42 (10.2)	30.17 (8.4) 36.17 (12.5)	0.99 0.37
iSP mean (% pre stim mean EMG)	Bilateral Unilateral	12 12	59.4 (8.8) 57.2 (9.7)	57.2 (5.8) 55.8 (10.7)	0.30 0.14	55.5 (6.9) 56.7 (7.9)	55.6 (7.1) 57.6 (11.9)	0.01 0.09
			Right APB Pre	**Right APB Post**		**Left APB Pre**	**Left APB Post**	
M_{max} (mV)	Bilateral Unilateral	12 12	14.83 (4.97) 15.40 (6.13)	14.57 (5.39) 14.10 (6.44)*	0.05 0.21	12.32 (3.99) 13.83 (4.69)	12.56 (3.81) 12.86 (3.72)*	0.06 0.23
H-reflex (% of m-wave)	Bilateral Unilateral	8 8	36.5 (9.8) 41.3 (18.4)	31.4 (13.6) 38.9 (16.1)	0.44 0.14	40.3 (21.7) 33.8 (18.5)	37.0 (14.7) 41.9 (15.7)	0.18 0.47

Table 2-3. Complete results.
n is sample size. SD is standard deviation. ES is effect size APB is abductor pollicus brevis. LH, left hemisphere; RH, right hemisphere; MVIC, maximal voluntary isometric contraction; MEP, motor-evoked potential; mV, millivolt; SICI, short interval intracortical inhibition; TS, test stimulus; CSP, contralateral silent period; iSP, ipsilateral silent period; EMG, electromyography; M_{max}, motor-wave max; H-reflex, Hoffmans reflex. Data is in mean ± SD. Data was analyzed with a two-way [TIME (T0, T1) X SIDE (Right, Left)] rmANOVA separately for each condition in each measure. * donates statistical significance across time $p \leq 0.05$.

2.3.5 Effect sizes

According to Rhea's 'Scale for determining the magnitude of ES in strength training research' ES were trivial or small at post-exercise compared to baseline for all of the strength measures.

For the bilateral condition, small ES were reported for MEPs. The ES for SICI were large for the LH (d=0.84) and small for the RH (d=0.37) even though the changes in SICI were significant post-exercise compared to baseline. For CSP the reported ES were small for both

hemispheres, despite a trend towards a shorter SP post-exercise (LH; *d*=0.32, RH; *d*=0.23). For TCI, the reported ES were larger for iSP duration, consistent with the trend towards less interhemispheric inhibition post-bilateral resistance exercise (LH; *d*=0.51, RH; *d*=0.99). Small ES were reported for M_{max} and H-reflex.

For the unilateral condition, the ES were small for MEPs. The ES were also small for SICI (LH; *d*= 0.24, RH; *d*=0.22). Small ES were also found for CSP (LH; *d*= 0.04 RH; *d*=0.13) and iSP duration (LH; *d*=0.06, RH; *d*=0.37). This is consistent with the significance found as no significant changes were found for the TMS neurophysiology measures post-exercise. Small ES were reported for M_{max} (Right APB; *d*=0.21, Left APB; *d*= 0.23), despite the significant decrease in M_{max} post-exercise. Small ES were also reported for H-reflex for the unilateral condition. Effect Sizes are reported in **Table 2-3.**

2.4 Discussion

The aim of the current study was to investigate the impact of an acute leg extension exercise bout, either bilaterally or unilaterally on corticospinal excitability in the cortical representation of the unexercised UE. This allowed us to determine the extent to which CE could influence corticospinal excitability changes beyond that of the exercised muscle and its homologous counterpart. This experiment showed that after the acute unilateral leg extension bout strength was improved in the exercised and unexercised leg. In addition, in the bilateral condition, there was a bilateral release of intracortical $GABA_A$ receptor related inhibition post-exercise and a non-significant trend towards both $GABA_B$ receptor related inhibition and interhemispheric inhibition decrease bilaterally after the acute exercise bout in the unexercised UE. In the unilateral condition, there was a depreciation in the M_{max} amplitude but no other

significant changes post-exercise in the unexercised UE compared to baseline. Lastly, changes in spinal excitability post-exercise were not found in either condition. Overall, this research shows that after an acute LE unilateral exercise bout the cortical impact of CE may be limited to homologous muscle groups. However, bilateral LE resistance exercise could be promising to influence cortical areas in the unexercised UE.

Aim 1: Changes in strength

After a bout of unilateral leg extensions, MVIC tests showed that the unexercised (left) leg had a 7.7% mean increase in strength and a 7.7% mean increase in strength in the exercised (right) leg. This amount of change was less than the recent meta-analysis that pooled CE studies with healthy individuals to show an average of an 11.9% increase in contralateral strength compared to pre-exercise. However, this analysis included studies where unilateral resistance exercise took place over extended periods of time compared to the current study that considered change after an acute exercise bout alone.[65] This improvement in strength was less than has been shown in previous CE studies with individuals with stroke.[24,25] This difference may be attributed to lower a baseline strength in individuals with stroke and enhanced neuroplastic potential in the brain post-stroke.[83] Acute sessions as well as training over time appear to both show contralateral improvements in strength after unilateral resistance exercise.[65,70] This may be applicable to clinicians when implementing exercise interventions to know that benefits are achieved after both long term and acute sessions.

Following bilateral exercise, strength increased in both legs (4.8% increase in right leg and 4.3% increase in left leg). Whether individuals exercised bilaterally or unilaterally there was an increase in strength post-exercise compared to baseline in both legs; this occurred even when the left leg was unexercised in the unilateral condition.

When looking at this MVIC data alone, it seems that CE benefits strength bilaterally. Even though changes in the central nervous system were investigated further, this is evidence that CE of strength was shown at a segmental, homologous level.

Aim 2: Corticospinal excitability changes after bilateral resistance exercise

Corticospinal excitability (indexed with MEPs at 130% of RMT) from bilateral APB did not change after the acute bout of bilateral resistance exercise. Past research that has detected increased excitability after bilateral resistance exercise however attributed this to a compensatory response to fatigued muscles[49,84]; in our study participants did not exercise to fatigue. However, we did note a release of intracortical inhibition (SICI). In addition, there was a trend towards a bilateral release of inhibition post-exercise in CSP and iSP duration. Given that this study was disrupted by the COVID-19 pandemic the full sample was not collected. To fully understand the impact of our CE intervention, effect sizes were calculated for CSP and iSP measures. Results demonstrated moderate and large effect sizes after exercise in the LH and RH, respectively for iSP duration. Small effect sizes were calculated for CSP. These trends should be interpreted cautiously considering the smaller than intended sample size and non-significant p-values.[85]

The bilateral acute exercise bout of leg extensions was selected based on Takahashi and colleagues (2011) study where participants performed resistance exercise followed by TMS measures of the unexercised UE. This past work provided evidence of LE resistance exercise in its ability to influence cortical regions of the non-exercised UE.[57] Takahashi and colleagues also found that following the acute fatigue-driven leg press intervention inhibition as measured through SICI was decreased, and a similar reduction in intracortical inhibition (SICI) was also found in this current study.[57] The current thesis and previous literature suggest evidence towards bilateral LE resistance exercise to influence the non-exercised UE and contribute to widespread

changes within M1 post-exercise. The decrease in intracortical inhibition in the unexercised UE could have been a result of intracortical connections present within M1 or global neuroplastic changes that occurred in motor cortices after bilateral exercise. This is similar to the idea of 'central adaptation' suggested by Cannon and Cafarelli that described a phenomenon where unexercised muscles benefit from global adaptations of motor patterns post-exercise which originate cortically. [86,87] An alternate hypothesis suggested by Rasmussen & colleagues is central oxygenation in the cortex by which inhibition release is as a result of fatigue in the brain post-exercise.[88] Byblow et al. have suggested that these connections between LE and UE may also be outside of M1, in secondary motor areas that facilitate nonspecific pathways between LE and UE areas; yet we did not investigate this possibility in this current study.[89] Further research that assesses bilateral resistance exercise at higher intensities would advance understanding of the impact of LE to UE transfer in M1 and secondary motor areas.

There were no changes in M_{max} amplitude in the unexercised UE. The lack of change in M_{max} is inconsistent with previous literature that showed an acute LE exercise bout decreased M_{max} measured after exercise.[56,84] Previous research however had participants perform training for bouts of longer durations using LE aerobic exercise rather than the resistance exercise bout employed in this thesis. Spinal excitability (H-reflex), also did not change following our intervention. Motl and Dishman (2003) noted that an acute bout of resistance exercise changed the H-reflex associated with the specific muscle used (soleus) post-exercise, but this finding did not generalize to other changes.[90] Taken together these data suggests that the transfer of effects noted in cortical excitability from LE to UE are likely mediated by brain rather than spinal mechanisms.

Aim 3: Corticospinal excitability changes after unilateral resistance exercise

In the current study there were no significant differences between pre and post-exercise in any of the TMS measures (MEP, SICI, CSP, TCI) for the unilateral condition in either hemisphere. Previous literature has shown that there are changes present in these measures when taken from the homologous muscle.[17,30,48] The stability of these measures suggests that the cortical impact of the CE may be limited to homologous muscles for acute sessions. Mason and colleagues (2017) found a similar cortical spatial confinement. In their work, changes to corticomotor excitability were only found in homologous muscles and not the unexercised/non homologous muscles after a 3-week unilateral training intervention.[91] The current study may suggest this same spatially confined transfer in M1.

The dose and intensity of the leg extensions performed in this study was based on two recent meta-analyses that investigated dose responses with the potential to influence both strength[70] changes as well as corticomotor excitability.[43] However, it is possible that the dose and intensity selected here was insufficient to generate a global effect on M1 and elicit this cross-over to be found in the unexercised UE. Hendy et al. (2017) suggests future studies administer the maximal intensity possible, specific to the LE to see corticomotor excitability changes specific to M1. [92]

There was a trend towards a release of inhibition in the right/unexercised hemisphere as measured through TCI and SICI that was not found in the exercised hemisphere. This observation only trended toward significance and small effect sizes were detected and as such should be interpreted cautiously.[81,85] Transcallosal inhibition and SICI showed this decrease in inhibition compared to the exercised hemisphere as expressed through a mean decrease in iSP duration and a mean increase in the amplitude of the conditioned stimulus relative to the test

stimulus in SICI. To explain this, a study by Lee and colleagues suggested that this release in inhibition could have occurred because the ipsilateral/ untrained M1 may be the driving force for the CE effects.[32,74] A recent systematic review also proposed that neural drive may actually originate in the untrained hemisphere, therefor the ipsilateral hemisphere would be responsible for acute transfer.[27] Stockel and colleagues may also denote this finding to distinct neural processes in the ipsilateral hemisphere during unilateral contractions that support the differences in cortical excitability seen in our research post-exercise.[93] The ipsilateral hemisphere has always contributed a crucial role in the inhibition of the exercised hemisphere[74,94] and this may be why this response may be seen in these inhibitory measures specific to the unexercised hemisphere.[27,74,95,96,97] Together, these findings suggest the importance of ipsilateral M1 in the strength changes seen after CE may account for the releases of inhibition post-exercise in the ipsilateral hemisphere.

The current study did show the minimal role, if any of spinal structures involved in this cross-body transfer after unilateral resistance exercise. There were no changes found in H-reflex in either APB at either time point. Past work also shows minimal changes in H-reflex are present post-exercise in unexercised muscles whether that be homologous or non-homologous.[37,90,98] Colomer-Poveda et al recommend that spinal changes require longer training duration (weeks) in order to see shifts in neural drive.[98]

Future studies

In the current study, unilateral LE resistance exercise did not affect cortical excitability or inhibition in the contralateral or ipsilateral M1 within the cortical representation of the unexercised UE or alter spinal reflexes in APB. There was however a significant increase in strength in the homologous unexercised limb in this study after unilateral LE resistance exercise.

This current research supports the effects of CE at the level of the exercised limb, suggesting the potential use of it in clinical practice. Previous literature that has investigated the impact of unilateral resistance exercise over longer durations also suggests the clinical relevance of incorporating CE as an intervention to endorse interhemispheric balance.[64,99] In future studies, unilateral resistance exercise dose and intensity in the LE should be amplified and cortical changes should be investigated at the level of the homologous muscle. Corticospinal changes at the level of the exercised limb were not investigated in this current study. It is possible that cortical changes in inhibition and excitability were occurring but not in the cortical representation of the APB muscle that was investigated.

2.5 Conclusion

In conclusion, the data presented here support the phenomenon of CE, where strength gains are seen on the exercised and unexercised side of the body in homologous limbs after unilateral resistance exercise.[15] However, our data also show that an acute bout of unilateral LE resistance exercise does not change corticospinal excitability in the cortical representation of the unexercised UE. However, the use of bilateral LE resistance exercise may prompt a bilateral intracortical release of inhibition in the unexercised UE. In addition, this research suggests that spinal mechanisms may not play a large role in the transfer of strength from LE to UE.

Future work should continue to explore the limits of CE over long-term trials, rather than acute sessions to see if more training is needed to detect changes in corticospinal excitability. In addition, exploring the use of CE in clinical settings, specifically stroke populations to advance understanding of the effect unilateral exercise using the non-paretic limb has on the ipsilateral

motor regions would be beneficial. Lastly, larger sample sizes should be used to achieve more conclusive evidence of CE in non-clinical as well as clinical populations.

3. Conclusions and General Direction

3.1 Introduction

The purpose of this current research was to determine whether the corticospinal excitability changes resulting from cross-education were confined to the bilateral spatial distribution of the exercised area of the primary motor cortex or if these changes affected the cortical representation of the unexercised brain regions. In order to test this question, 12 participants between the ages of 19 and 36 performed bilateral and unilateral leg extension exercises on two separate days and neurophysiology measures were collected from the untrained abductor pollicus brevis muscles. On each day, participants' baseline (T0) and post-exercise (T1) strength and neurophysiology outcome measured were collected.

3.2 Summary of the findings

3.2.1 Acute resistance exercise in the lower extremity and the effects on corticospinal excitability in the unexercised upper extremity.

Unilateral resistance exercise in healthy adults increases strength and releases intracortical (SICI) and corticospinal (CSP) inhibition within contralateral homologous muscles.[17,48] Previous work by Takahashi and colleagues (2011) showed transfer of corticospinal excitability and release of intracortical inhibition in the unexercised UE after an acute bout of bilateral LE resistance exercise.[57] Currently, evidence is inconclusive on whether cross-education can be transferred to non-homologous muscles and whether bilateral cortical regions are affected beyond those of the trained limb.[61,91] Furthermore, the cortical spatial distribution of cross-education from LE to UE after resistance exercise has been sparsely investigated.[55,56,57]

Results from this experiment (**Chapter 2**) showed that cross-education of strength can be transferred to the unexercised, homologous limb after an acute exercise bout of unilateral leg extension exercises; this is consistent with existing literature.[15,65] Bilateral LE resistance exercise was accompanied by a decrease in $GABA_A$ related inhibition in the unexercised UE but further testing with a different training dose and intensity and larger sample size may be needed to see significant releases of $GABA_B$ mediated inhibition and interhemispheric inhibition. Cross-education after unilateral resistance exercise may be mediated cortically at the level of homologous limb[60]; this current research suggests these changes may be confined, and not applicable to other ipsilateral and contralateral muscles and their respective motor regions. This suggests a spatially distinct element of cross-education through which corticomotor changes are only seen in the opposite muscle that was exercised.

3.3 Limitations

This study has several limitations. The first was the inability to elicit an H-reflex response on the EMG for every participant in this thesis sample (*n=8*). The result of this limitation was that this study has lower power to detect change in spinal structures. Future research should consider examination of the spinal contribution to cross-education.[24,37]The H-reflex data we did collect however, suggests that the bulk of change was cortical rather than spinal in nature.

Secondly, although this current study considered corticospinal excitability changes within the cortical representation of the unexercised UE, this study did not investigate corticospinal excitability changes within the exercised LE. Further, if changes were seen in the LE regions but not in UE regions, it may encourage further cross-education research to focus on cross-over that occurs between homologous muscles only. The purpose of this work however was to address the

corticospinal changes specifically in the unexercised muscles as the corticospinal effects of cross-education have already been shown in homologous muscle pairs.

Thirdly, the dose and intensity of the leg extension exercise followed previous research, but it is possible that it was not enough to elicit corticospinal excitability changes, or that it only conferred a transient change. It has been suggested that a maximal intensity or a fatigue-driven form of resistance exercise needs to be administered for cross-body[57] and cross-over.[92] corticospinal changes within M1 to occur in the LE. Considering fewer cross-education studies have been conducted in the lower extremity, this current work suggests that the dose allocated to participants may be different in the LE than in the UE and future work should administer higher doses and intensities.

Another limitation to consider is the absence of a non-exercising control group. The addition of a non-exercising condition would have allowed for a comparison between neurophysiology measures after exercise versus after a sedentary intervention. However, because this was a within subject study design participants acted as their own control with baseline measures taken on day one and day two. Using a paired samples T-test, day one and day two baselines were compared and there were no significant differences between the neurophysiology measures at baseline for the participants (p>0.05).

Lastly, a major limitation of this study was that it did not meet its recruitment goal of 15 participants. In mid-March 2020, the COVID-19 pandemic forced labs and workspace in British Columbia to shut down during the mandatory quarantine period. For this reason, the sample size of this study was not as large as intended and the study was unable to be completed in its entirety by the end of this Master's degree. To mitigate this limitation, effect sizes were calculated to

supplement *p*-values to better understand the magnitude of changes that may have occurred as a result of the intervention.[81,82]

3.4 Conclusions and future directions

This current thesis has paved the way for future research with cross-education. Additional research that investigates 'cross-body' transfer from the LE to the UE with a larger sample size is recommended to further evaluate the consistency of releases in cortical inhibition post-exercise.

TMS outcome measures were used in this study to evaluate neurophysiology changes. It may be important in future cross-education research to collect information about neuroplasticity through alternative measures. As an example, neuroimaging including functional magnetic resonance imaging (fMRI) may be useful to investigate cross-education further by looking at ipsilateral cortical changes during and after unilateral movement.[33] This in addition to other devices such as electroencephalography could help to better characterize brain activity after unilateral movement.

Resistance exercise can help improve motor function and therefore overall quality of life in individuals who have had a stroke. Investigating novel exercise interventions for paretic and non-paretic limbs that can optimize neuroplastic recovery post-stroke is essential in advancing stroke rehabilitation research. Specifically, if there are cortical benefits that contribute to normalizing IHI after resistance exercise with the non-paretic limb this would allow individuals with stroke to optimize corticomotor responses even when the paretic limb is paralyzed, stiff or spastic. Cross-education research can also be beneficial to health care workers who work with individuals undergoing neurorehabilitation to be less hesitant towards supporting exercise with both limbs and not just the paretic. Clinically, continued research that investigates the magnitude of the effects certain resistance training exercises could have on motor areas in the brain could

help to optimize resistance exercise interventions to achieve the best neuroplastic development to improve motor function after stroke.

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Appendices

Appendix A: Transcranial magnetic stimulation screening form

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.

_____
_____

Version Date: January 10, 2012

Appendix B: Physical activity readiness questionnaire plus

2018 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it ***does not limit your current ability*** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION
If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness centre may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

01-11-2017

2018 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you currently have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? *This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm*

If the above condition(s) is/are present, answer questions 3a-3d — If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have High Blood Pressure?

If the above condition(s) is/are present, answer questions 4a-4b — If **NO** ☐ go to question 5

4a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
4b.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐

5. Do you have any Metabolic Conditions? *This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes*

If the above condition(s) is/are present, answer questions 5a-5e — If **NO** ☐ go to question 6

5a.	Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies?	YES ☐ NO ☐
5b.	Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.	YES ☐ NO ☐
5c.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet?	YES ☐ NO ☐
5d.	Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)?	YES ☐ NO ☐
5e.	Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future?	YES ☐ NO ☐

2018 PAR-Q+

6. **Do you have any Mental Health Problems or Learning Difficulties?** *This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome*

If the above condition(s) is/are present, answer questions 6a-6b — If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	**YES** ☐ **NO** ☐
6b.	Do you have Down Syndrome **AND** back problems affecting nerves or muscles?	**YES** ☐ **NO** ☐

7. **Do you have a Respiratory Disease?** *This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure*

If the above condition(s) is/are present, answer questions 7a-7d — If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	**YES** ☐ **NO** ☐
7b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	**YES** ☐ **NO** ☐
7c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	**YES** ☐ **NO** ☐
7d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	**YES** ☐ **NO** ☐

8. **Do you have a Spinal Cord Injury?** *This includes Tetraplegia and Paraplegia*

If the above condition(s) is/are present, answer questions 8a-8c — If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	**YES** ☐ **NO** ☐
8b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	**YES** ☐ **NO** ☐
8c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	**YES** ☐ **NO** ☐

9. **Have you had a Stroke?** *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event*

If the above condition(s) is/are present, answer questions 9a-9c — If **NO** ☐ go to question 10

9a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	**YES** ☐ **NO** ☐
9b.	Do you have any impairment in walking or mobility?	**YES** ☐ **NO** ☐
9c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	**YES** ☐ **NO** ☐

10. **Do you have any other medical condition not listed above or do you have two or more medical conditions?**

If you have other medical conditions, answer questions 10a-10c — If **NO** ☐ read the Page 4 recommendations

10a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	**YES** ☐ **NO** ☐
10b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	**YES** ☐ **NO** ☐
10c.	Do you currently live with two or more medical conditions?	**YES** ☐ **NO** ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

_____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

2018 PAR-Q+

If you answered NO to all of the FOLLOW-UP questions (pgs. 2-3) about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

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Citation for PAR-Q+
Warburton DER, Jamnik VK, Bredin SSD, and Gledhill N on behalf of the PAR-Q+ Collaboration. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). Health & Fitness Journal of Canada 4(2):3-23, 2011.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

Key References

1. Jamnik VK, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the effectiveness of clearance for physical activity participation; background and overall process. APNM 36(S1):S3-S13, 2011.
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3. Chisholm DM, Collis ML, Kulak LL, Davenport W, and Gruber N. Physical activity readiness. British Columbia Medical Journal. 1975;17:375-378.
4. Thomas S, Reading J, and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Canadian Journal of Sport Science 1992;17:4 338-345.

01-11-2017

Appendix C. Cross-education screening questionnaire

Cross-Education Screening Questionnaire

Participant ID: Date:

What side is your dominant arm and leg?

Right Left

Do you have a history of any neurological disorders?

YES NO

If yes elaborate:

_____
_____

Do you have a history of any knee surgery and/ or knee injuries?

Yes No

If yes elaborate:

_____
_____

Have you ever had substance abuse such as alcohol or drugs?

Yes No

If yes elaborate:

_____
_____

Is there any reason that you can think of that would put you at any risk for exercise participation?

Yes No

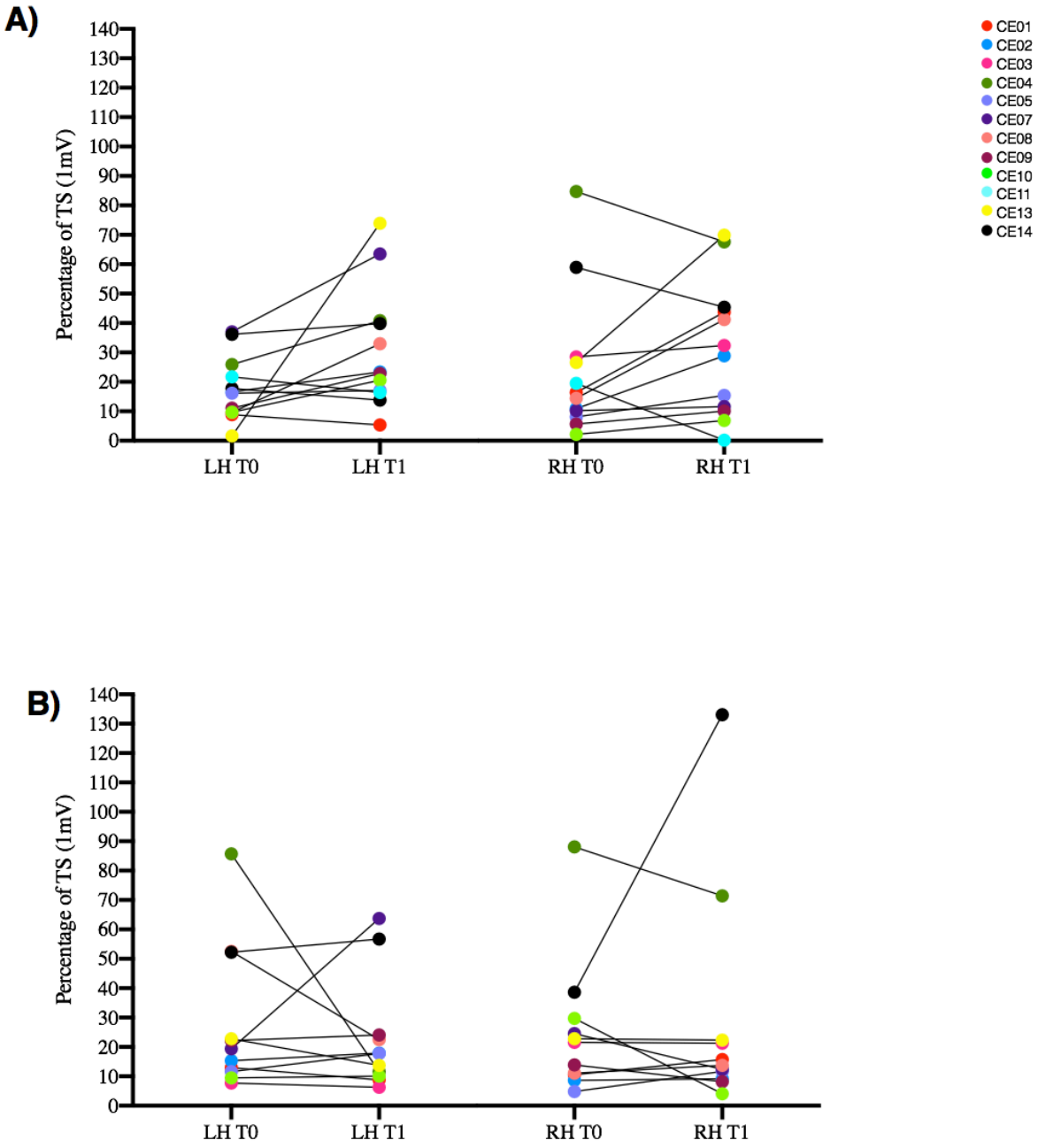
If yes elaborate:

_____
_____

Version 1: July 23, 2019

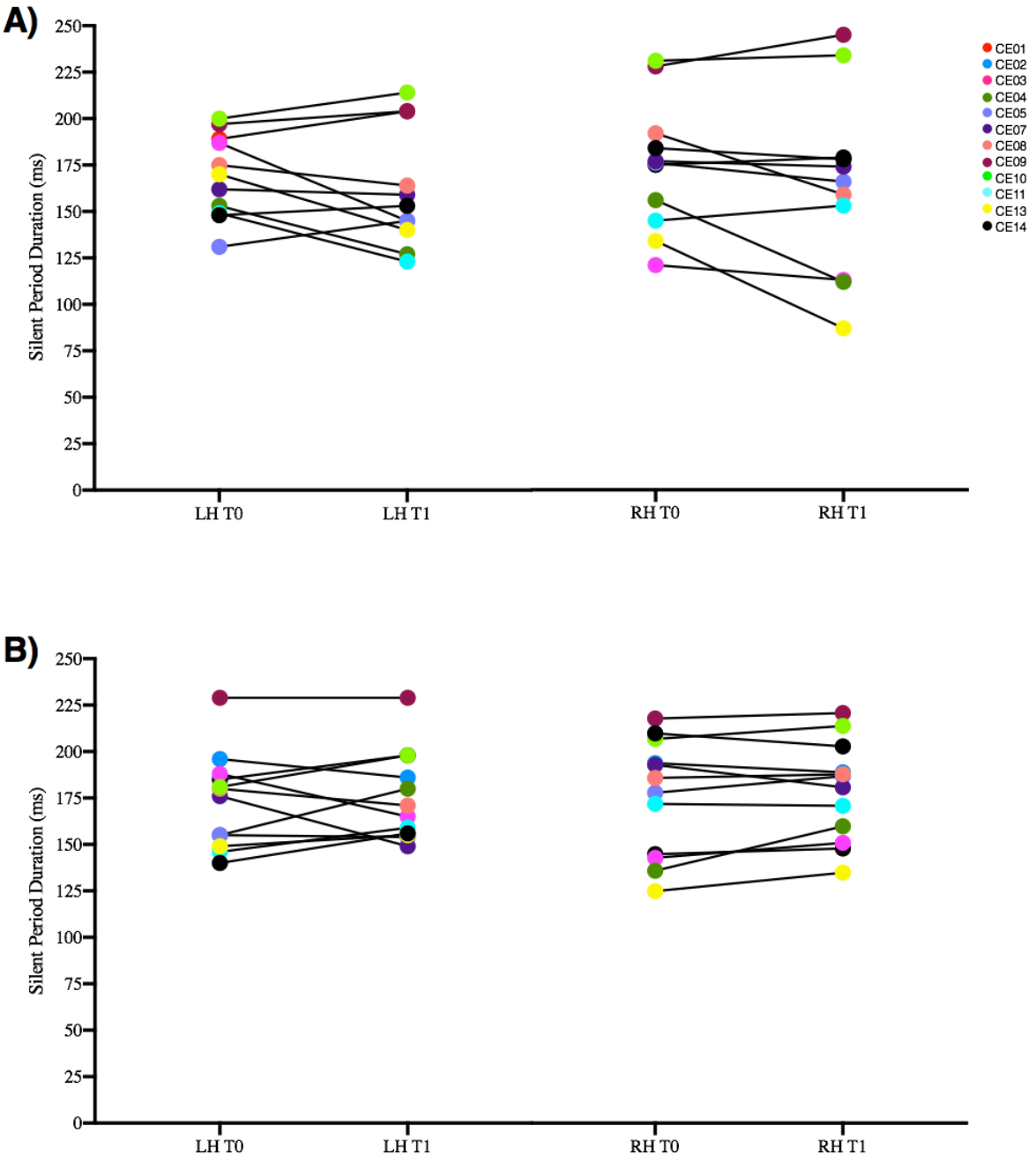
Appendix D: Supplementary graphs

Figure D-1. SICI individual data



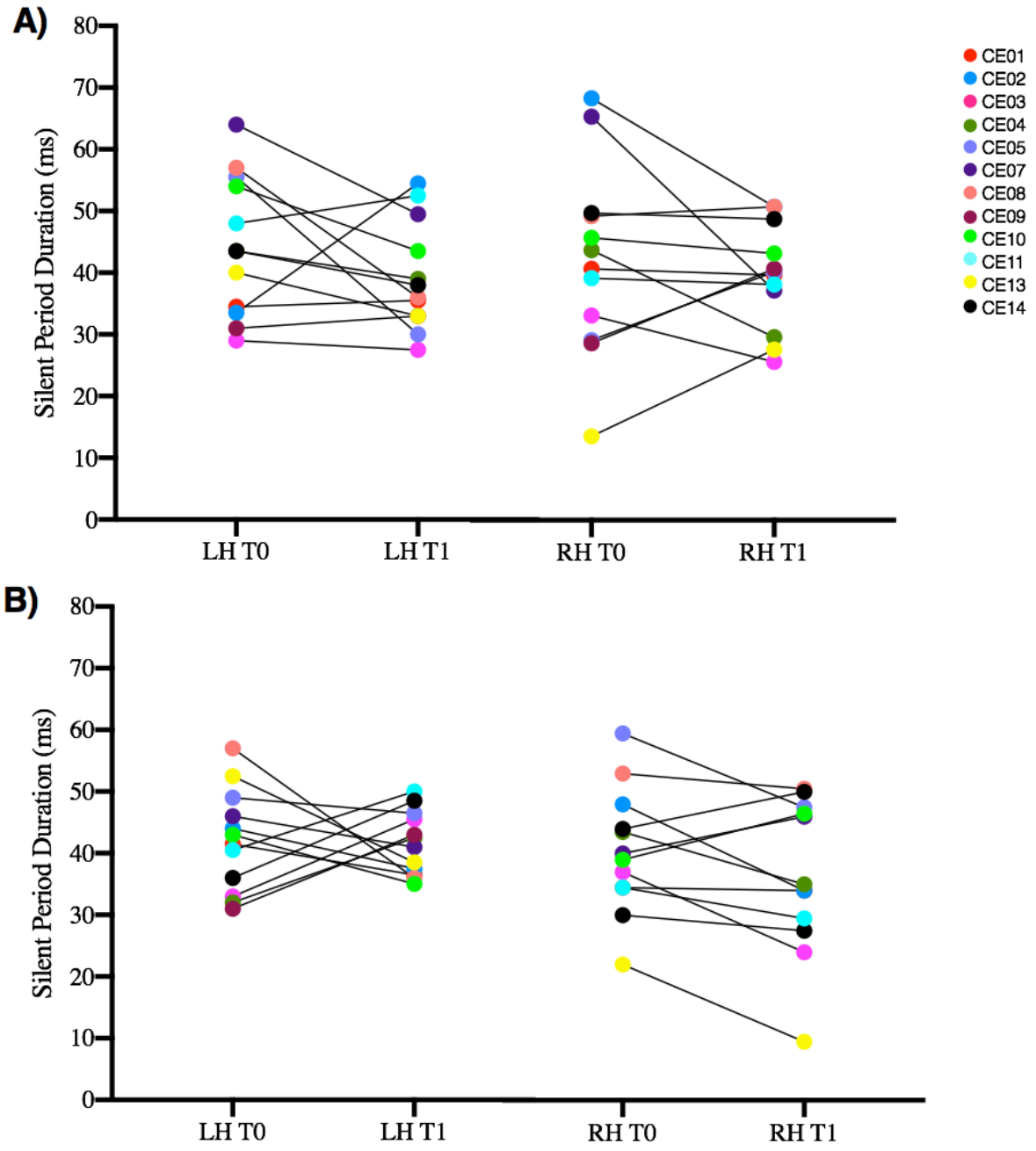
Each point donates the SICI value of an individual participant. RH, right hemisphere; LH, left hemisphere. T0 is baseline, T1 is post-exercise. Higher values indicate less inhibition. Each colour represents an individual participant. A) Bilateral condition (*n*=12) B) Unilateral condition (*n*=11) the LH is the exercised hemisphere and the RH is the unexercised.

Figure D-2: CSP individual data



Each point donates the CSP duration of an individual participant. RH, right hemisphere; LH, left hemisphere, T0 is baseline, T1 is post-exercise. Lower values indicate less inhibition. Each colour represents an individual participant A) Bilateral condition (*n*=11) B) Unilateral condition (*n*=12) the LH is the exercised hemisphere and the RH is the unexercised.

Figure D-3: iSP duration individual data



Each point donates the iSP duration of an individual participant. RH, right hemisphere; LH, left hemisphere, T0 is baseline, T1 is post-exercise. Each colour represents an individual participant. Lower values indicate less inhibition A) Bilateral condition (*n*=12) B) Unilateral condition (*n*=12) the LH is the exercised hemisphere and the RH is the unexercised.