THE IMPACT OF AN ACUTE BOUT OF HIGH INTENSITY EXERCISE ON CORTICOSPINAL EXCITABILITY AND TRANSCALLOSAL INHIBITION IN OLDER ADULTS

by

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Abstract

While studies have investigated the effect of exercise on corticospinal, intracortical, and interhemispheric processes in young adults, few studies have focused on older adults. Current evidence supports the hypothesis that there is a shift from predominantly inhibitory to excitatory interhemispheric interactions as we age. Other work suggests that changes observed in transcallosal inhibition (TCI) with age (i.e., reduced ipsilateral silent period (iSP) duration and area) may be mitigated by physical activity. Therefore, the main purpose of this experiment was to advance understanding of how an acute bout of high intensity exercise alters patterns of corticospinal and interhemispheric excitability in the healthy older adult population.

41 healthy older adults participated in this study. Participants were randomized into the exercise (n=21) or the rest (n=20) group. Participants in the exercise group completed an acute bout of high intensity exercise on a recumbent bike lasting 23 minutes. Participants in the rest group sat for the same duration of time while their attention was controlled by watching a nature documentary. Corticospinal excitability and TCI of the upper limbs was assessed via transcranial magnetic stimulation before (baseline), immediately (Post 1), and 30 minutes (Post 2) following high intensity exercise or rest.

Results indicated that there was an increase in corticospinal excitability immediately and 30 minutes post exercise in the dominant hemisphere. There was also an interaction effect between timepoint and hemisphere in transcallosal inhibition.

The current study showed following an acute bout of high intensity exercise, there was an increase in corticospinal excitability in the dominant hemisphere and a hemispheric difference in TCI in older adults. The present research provides insight on how exercise could be used to

mitigate age related changes in the brain and informs how exercise therapies could be employed in association with rehabilitation in clinical populations.

Lay Summary

Brain excitability and relationships between various brain areas change as we age. Exercise has been shown to promote adaptive changes in the brain in young adults but there is little research on how exercise impacts brain plasticity in older adults. In the present study, a single session of high intensity exercise was performed by older adults. Various measures that indicate brain plasticity including brain and spinal excitability, and how the two halves of the brain inhibit each other, were measured using non-invasive brain stimulation before, immediately after exercise, and 30 minutes after exercise. The results indicate that a single session of high intensity exercise impact brain excitability in older adults. These findings provide us a better understanding of how exercise influences the brain, and how that may be applied to clinical populations with age-related disorders.

Preface

The present thesis has been completed by Briana Chau under the supervision of Dr. Lara Boyd. The experimental design was a joint effort between the supervisor, Dr. Jason Neva, Dr. Brian Greeley, and me. I collected data with assistance from Dr. B. Greeley, C. Jones, J. Ferris, and R. Denyer. Data processing, statistical analysis, and documentation were done primarily by me. Data from the current thesis will be submitted for publication in the future.

The present study was approved by University of British Columbia's Clinical Research Ethics Board (certificate #H16-01945), and conducted primarily in the Brain Behaviour Laboratory at the University of British Columbia Vancouver campus.

Figures from published manuscripts were adapted in the current thesis (Chapter 1). **Figure 1-1** is accessible through Open Access. Permission to re-use **Figures 1-2, 1-3, and 1-4** have been granted by their respective journals.

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List of Abbreviations

ANOVA: Analysis of Variance

AUC: Area under the curve

DTI: Diffusion tensor imaging

ECR: Extensor carpi radialis

EMG: Electromyography

FA: Fractional anisotropy

GABA: γ- Aminobutyric Acid

$GABA_A$: GABA receptor subtype A

$GABA_B$: GABA receptor subtype B

HAROLD: Hemispheric asymmetry reduction in older adults

ICF: Intracortical facilitation

IHI: Interhemispheric inhibition

ISI: Interstimulus interval

iSP: Ipsilateral silent period

LICI: Long-interval intracortical inhibition

M1: Primary motor cortex

MEP: Motor evoked potential

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

ms: millisecond

MSO: Maximum stimulator output

MVC: Max voluntary contraction

MWF: Myelin water fraction

PAS: Paired Associative Stimulation

Post 1: Immediately after exercise protocol

Post 2: 30 minutes after exercise protocol

RMT: Resting motor threshold

RPE: Rate of perceived exertion

RPM: Revolutions per minute

SEM: Standard error of mean

SICI: Short-interval intracortical inhibition

TCI: Transcallosal inhibition

TMS: Transcranial magnetic stimulation

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And of course, I would like to say a big thank you to my family for supporting me. And to my friends, you all know who you are. Thank you for being there since day 1.

Chapter 1: Introduction

1.1 General introduction

Neuroplasticity describes the ability of the brain to adapt and change. Studies have shown that exercise facilitates neuroplasticity, and can also modulate cognition and behaviour. Exercise benefits declarative learning, processing speed, and cognitive flexibility (Winter et al., 2007; Masley et al., 2009; Kamijo et al., 2007). Recent work shows that exercise also benefits the learning of new movements; pairing short bouts of high intensity cycling exercise with skilled motor practice improves motor memory consolidation of skilled upper-limb tasks (Mang et al., 2014, 2016), and alters intrahemispheric and interhemispheric cortical excitability (Mang et al., 2014; Neva et al., 2017).

Much of the work surrounding the effects of exercise on patterns of cortical excitability considered only young healthy adults. Therefore, **the main aim of this thesis is to advance understanding of how high intensity intervals of exercise alter patterns of cortical and interhemispheric excitability in the healthy older adult population**. Specifically, this thesis will investigate whether an acute bout of high intensity aerobic exercise affects corticospinal excitability and interhemispheric inhibition in older adults aged 50 to 90. The following section will provide an overview of important concepts that are relevant for this thesis, and provide the rationale behind each specific aim.

1.1.1 Assessing corticospinal excitability using non-invasive neurostimulation

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique used to target regions of the brain with electromagnetically induced currents (Rossini et al., 1994). This method is useful when studying neurophysiological circuits of the brain (Rossini & Rossi, 2007). A TMS pulse over the hand representation on the primary motor cortex (M1)

produces a muscle twitch in the contralateral hand muscle. Electromyography (EMG) is used to quantify these muscle twitches which produce a waveform, called a motor evoked potential (MEP). MEPs are characterized by quantifying their peak-to-peak amplitudes (Neva et al., 2017). MEP recruitment curves generated by delivering stimulation at varied intensities over the primary motor cortex for target muscles can be generated to quantify corticospinal excitability (Wassermann et al., 1998). Resting motor threshold (RMT) is first determined as the lowest stimulation intensity to evoke MEPs of at least 50 μV in 5 out of 10 consecutive trials (Rothwell et al., 1999). Various percentages of RMT determine the stimulation intensities to obtain the MEP recruitment curve.

Our voluntary limb movements are dependent on the ability of the brain to communicate with target muscles in our periphery. Decades of research show that TMS can be used to probe and alter the excitability of the cortex. For instance, low frequency repetitive TMS (1Hz) depresses motor cortex excitability (Gerschlager et al., 2001; Chen et al., 1997; Wassermann et al., 1998). Alternatively, stimulation at >5 Hz has a faciliatory effect on corticospinal excitability (Maeda et al., 2000). TMS can also be used to monitor the impact of interventions on cortical excitability. For example, the use of dopaminergic and anti-dopaminergic drugs alters motor cortex excitability (Ziemann et al., 1997), revealing that excitability is modulated by dopaminergic fibers in the brain.

Using TMS to assess corticospinal excitability has proven to be a useful tool in various neurological conditions such as multiple sclerosis, amyotrophic lateral sclerosis, stroke, epilepsy, and dystonia (Di Lazzaro et al., 1999; Curra et al., 2002). Specifically, TMS produced MEPs provide an objective measure of corticospinal tract integrity which is clinically important for individuals with movement disorders (Cantello, 2002) and after stroke (Boyd et al., 2017).

Altered or absent corticospinal excitability early after stroke is predicts poor recovery (Rossini et al., 2003; Stinear et al., 2012) and can be mapped in the acute hospital setting to inform clinical care (Stinear et al., 2017).

Motor learning is another field in which corticospinal excitability has been studied using TMS. The primary motor cortex plays a key role in mediating learning related changes (Muellbacher et al., 2001). Corticospinal excitability increases after practice of novel motor skill and skilled motor training (Pascual-Leone et al., 1995; Jensen et al., 2005), indicating the importance of these neuroplastic changes in motor learning. Neuroplastic changes associated with learning illustrates that this process involves strengthening of existing neural connections, and the formation of novel connections that support skill learning (Hosp & Luft, 2011). Interestingly, it has also been shown that in individuals with stroke corticospinal excitability increases after repetitive movements that do not require learning (Stinear et al., 2008). Thus, in the context of applying research to clinical populations, including those with motor impairments, studying the relationship between corticospinal excitability and motor learning is critical.

1.1.2 Assessing intracortical and interhemispheric interactions using non-invasive neurostimulation

TMS can also be administered in paired pulses to assess the excitability of interneuronal circuits in the motor cortex. These approaches can map intracortical excitability or interhemispheric interactions. During intracortical mapping pairs of TMS pulses are separated by a short time period, known as the interstimulus interval (ISI). For example, short-interval intracortical inhibition (SICI) is measured by delivering two TMS pulses 2-5 milliseconds apart; this provides information on inhibitory intracortical circuits (Wagle-Shukla et al., 2009). Long-interval intracortical inhibition (LICI) is measured by delivering paired pulses 50 to 200 ms apart (McNeil et al., 2011). When pairs of pulses are separated by longer periods of time (>12 ms)

intracortical facilitation (ICF) can be mapped (Ortu et al., 2008). These measures reflect various forms of neurochemical signalling which are important for understanding neurophysiological circuits.

TMS may also be used to study interhemispheric interactions. Previous work established the importance of interhemispheric communication in producing upper-limb movements (Fleming & Newham, 2017). Bilateral activation of the primary motor cortex in healthy people occurs even during unilateral limb movement (Chiou et al., 2013; Kim et al., 1993; Alkadhi et al., 2002). Producing unilateral motor movement requires more interhemispheric interactions between cortical areas compared to symmetrical bimanual movement which have a tendency to synchronize (Cincotta & Ziemann, 2008; Swinnen et al., 1991). Thus, execution of a unilateral motor movement requires the restriction of motor output to the contralateral M1 to the hand of the intended movement (Beaule et al., 2012). It is via the pathways in the corpus callosum that the primary motor cortices (M1) in each hemisphere interact with each other at the cortical level to facilitate both unimanual and bimanual movements (Meyer et al., 1995; Hubers et al., 2008; Ferbert et al., 1992; Boroojerdi et al., 1996). Transcallosal connections can be facilitatory, however, mutual inhibition is the primary interaction between the two cortices (De Gennaro et al., 2004). Early work showed that mutual transcallosal inhibition (TCI) of the motor cortices is mediated by fibers passing through the posterior half of the trunk of the corpus callosum (Meyer et al., 1995). Ultimately, this mutual inhibition contributes to both unilateral limb movement due to increased inhibitory drive from the active hemisphere and bilateral actions due to more balanced inhibition between hemispheres which leads to coordination (Fling et al., 2012; Shim et al., 2005). See **Figure 1-1**.

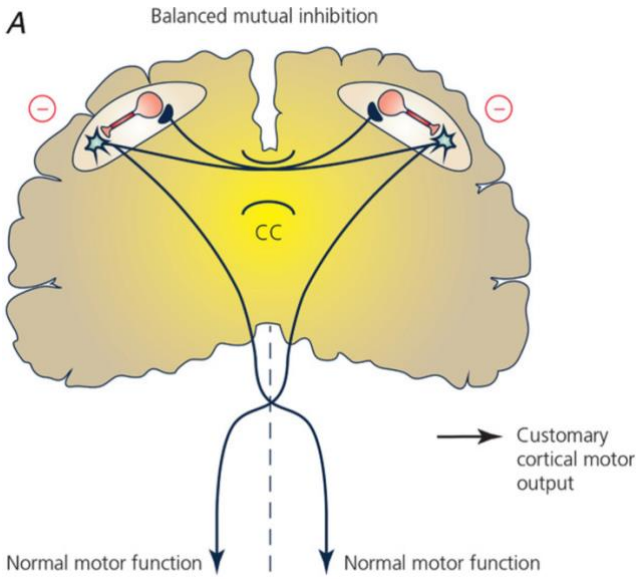


Figure 1-1. Balanced mutual inhibition.
Adapted from Carson (2020). Illustration of mutual inhibition between the two motor cortices that give rise to efferent projections onto motor neurons innervating the homologous muscles of the opposite limb.

To assess interhemispheric interactions and transcallosal inhibition, TMS is applied over M1 at a suprathreshold intensity during voluntary contractions (Chen et al., 2003). This provides information about the amount of inhibition that one hemisphere has over the other by quantifying interhemispheric inhibition (IHI) and ipsilateral silent period (iSP). Interhemispheric inhibition is measured as a reduction in corticospinal excitability evoked when a conditioning stimulus is applied at a suprathreshold stimulus a short inter-stimulus interval (typically between 9 and 12 ms) before a test stimulus is applied at a suprathreshold stimulus over the contralateral hemisphere (Chen et al., 2003; Ibey et al., 2015). The iSP is assessed by applying a single pulse of TMS over the motor cortex ipsilateral to the test hand while activating the target muscle (Davidson & Tremblay, 2013). The TMS pulse briefly interrupts voluntary muscle activity in the contralateral hand, which is mediated by the primary motor cortex contralateral to the active muscle (Meyer et al., 1995). TCI is typically quantified using iSP characteristics. See **Figures 1-2 and 1-3**.

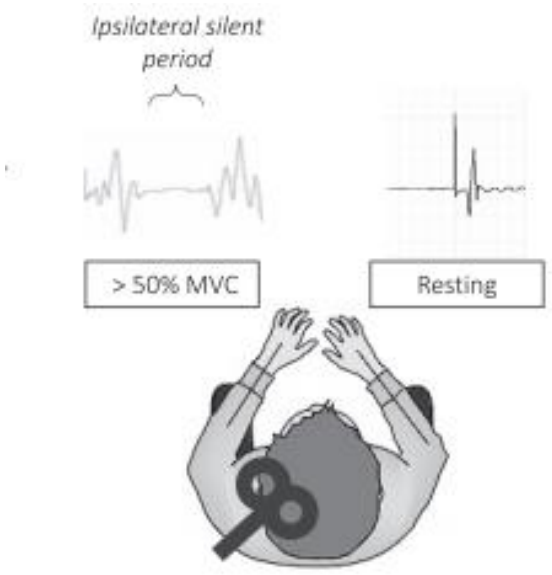


Figure 1-2. Using TMS to assess ipsilateral silent period.
Visual adapted from Cabibel et al. (2020) depicting TMS over left M1. In this set up, the left arm contracts at 50% MVC while the right arm stays at rest during stimulation, resulting in a disruption of the continuous muscle activity in the left arm shown by the ipsilateral silent period.

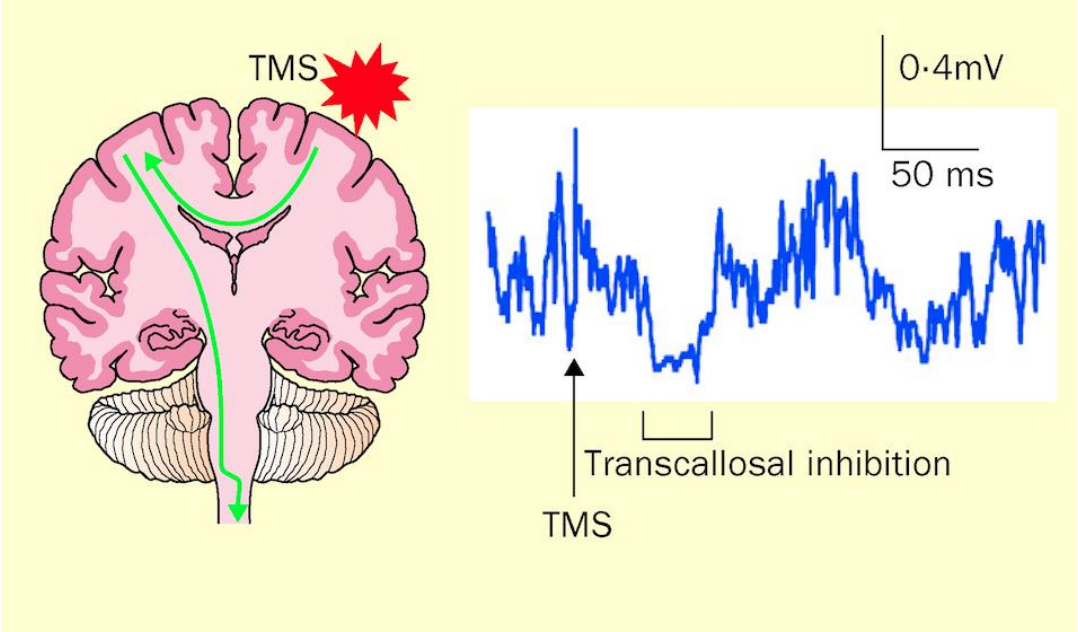


Figure 1-3. Transcallosal inhibition during TMS stimulation.
Adapted from Kobayashi & Pascual-Leone (2003) illustrating the transcallosal inhibition from right to left M1. The EMG shows the right arm's disrupted muscle activity after stimulation, indicating transcallosal inhibition occurring.

1.1.3 Exercise and its effects on neuroplasticity in healthy young adults

Aerobic exercise influences the brain through catecholamines and neurotrophic growth factors, both of which are increased after a bout of aerobic exercise (Winter et al., 2012; Chowdhury et al., 2012; Skriver et al., 2014; Knaepen et al., 2010; Cahill & Alkire, 2003). Recent studies have used non-invasive brain stimulation techniques, such as TMS, to investigate whether single bouts of either high or moderate intensity aerobic exercise alter M1 neuroplasticity in young healthy people and if these changes can be categorized using TMS (Singh et al., 2014a; Mang et al., 2014; McDonnell et al., 2013; Neva et al., 2017). High intensity exercise can be conducted with an interval training method. High intensity interval exercise can be differentiated from moderate or low intensity exercise by the greater rate of energy supply required within the muscles being exercised; the increased rate is greater than the rate at which glycogen can be broke down resulting in an increased reliance on anaerobic glycolysis and lactate accumulation (Stavrinos & Coxon, 2017). Moderate intensity exercise can be performed in a continuous manner, with participants maintaining 65-70% of their age-predicted maximal heart rate throughout the session (Neva et al., 2017). Altogether, acute aerobic exercise appears to affect neuroplasticity in humans by impacting the modulation of M1 excitability in nonexercised muscles (Singh et al., 2014a; Mang et al., 2014; McDonnell et al., 2013).

An acute bout of lower body aerobic exercise (Singh et al., 2014a, Neva et al., 2017), however, has differential effects on plasticity in the corticospinal tract depending on exercise intensity (Singh et al., 2014a; Mang et al., 2014). While MEP recruitment curves obtained from single-pulse TMS in hand muscles do not change after moderate (Smith et al., 2014; Singh et al., 2014a, Brown et al., 2020) or low intensity aerobic exercise (McDonnell et al., 2013), high intensity aerobic exercise increases corticospinal excitability, as measured in a paired associative

stimulus (PAS) paradigm (Mang et al., 2014). PAS consists of slow-rate repetitive low frequency median nerve stimulation paired with TMS over the contralateral motor cortex (Classen et al., 2004). Additionally, it appears that intracortical excitability within the M1 hand muscle representation is altered by acute bouts of aerobic exercise. An acute bout of moderate intensity aerobic exercise modulates intracortical excitability via increases in short-interval intracortical facilitation (SICF) and decreases in SICI (Smith et al., 2014, Singh et al., 2014a). LICI, however, does not seem to be affected by single bouts of aerobic exercise in young adults (Singh et al., 2014a). See **Table 1-1** for summary.

The finding that SICI and SICF are altered immediately following high (Andrews et al., 2020) or moderate intensity (Smith et al., 2014; Singh et al., 2014a) exercise has prompted further research into how aerobic exercise affects various cortical circuits, specifically, intracortical and interhemispheric excitability (Neva et al., 2017). SICI, SICF, and LICI, all represent local intracortical circuits in M1 (Kujirai et al., 1993). The former is thought to be $GABA_A$ mediated, whereas the latter is thought to reflect $GABA_B$ receptor activity (Ziemann et al., 1996; McDonnell et al., 2006). Evidence from pharmacological studies have shown lorazepam, a $GABA_A$ agonist, increases SICI and completely suppresses SICF (Ziemann et al., 1996). Another study showed ingestion of baclofen, a $GABA_B$ agonist, increased LICI (McDonnell et al., 2006).

Although there is evidence explaining the neurophysiological basis behind SICI, SICF, and LICI, the neurophysiological underpinnings of TCI are currently not well understood. A possible hypothesis suggests that interhemispheric inhibition interacts with intracortical measures of inhibition, such as LICI and SICI (Udupa et al., 2010; Chen, 2003; Daskalakis et al.,

2002). Udupa and colleagues (2010) found that both interhemispheric inhibition and LICI are reduced in the presence of each other. This indicates that interhemispheric inhibition and LICI share a common circuitry. The researchers hypothesize that interhemispheric interaction inhibits LICI through $GABA_B$ receptors but with the $GABA_{B1a}$ isoform. Daskalakis et al. (2002) showed that SICI was significantly reduced in the presence of interhemispheric inhibition as well.

Because acute exercise changes local intracortical inhibitory networks it is likely that it also influences transcallosal projecting neurons, which can be measured by TCI. Recent evidence showed TCI decreased bilaterally after an acute session consisting of 20 minutes of moderate intensity lower limb cycling exercise in healthy young adults (Neva et al., 2017). In this work TCI was quantified using iSP duration and area under the iSP curve. See **Figure 1-4**.

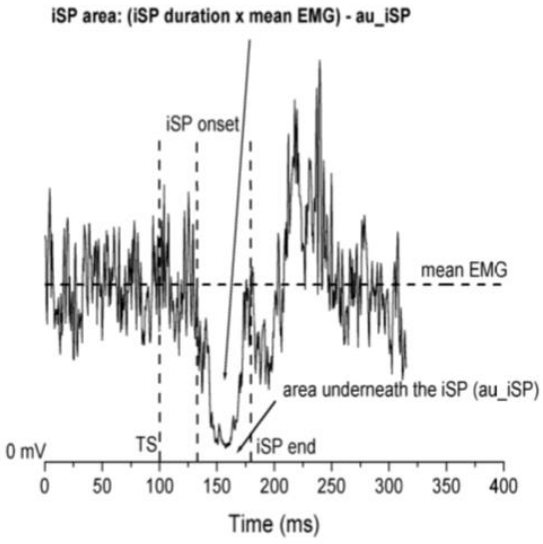


Figure 1-4. Characteristics of the iSP.
Adapted from Trompetto et al. (2004). A processed trial to quantify various iSP characteristics. Horizontal dashed line: mean pre-TMS EMG. The labels depict the TS (when TMS is triggered), iSP onset, iSP end (offset), iSP area, and area under the iSP curve.

	Type of Exercise	TMS Measures	Changes Post Exercise
Mang et al., 2014	High intensity	MEPs (PAS)	MEPs ↑
Andrews et al., 2020	High intensity	MEPs	MEPs ↑
		SICI	SICI ↓
		SICF	SICF ↑
		LICI	LICI –
	Moderate intensity	MEPs	MEPs –
		SICI	SICI –
		ICF	ICF –
		LICI	LICI –
Brown et al., 2020	Moderate intensity	MEPs	MEPs –
Smith et al., 2014	Moderate intensity	MEPs	MEPs –
		SICI	SICI ↓
Singh et al., 2014a	Moderate intensity	MEPs	MEPs –
		SICI	SICI ↓
		LICI	LICI –
		SICF	SICF ↑
Neva et al., 2017	Moderate intensity	MEPs	MEPs –
		SICF	SICF ↑
		iSP	iSP ↓
McDonnell et al., 2013	Low intensity	MEPs	MEPs –

Table 1-1. Summary of studies on acute exercise and its effects on TMS measures in healthy young adults.

1.1.4 Corticospinal excitability & transcallosal inhibition in healthy older adults

While studies have investigated the effect of exercise on corticospinal, intracortical, and interhemispheric processes in young adults, there have been fewer examinations of the same questions in older adults. Current ideas surrounding the impact of aging stem from paired-pulse TMS studies designed to consider intracortical excitability. Healthy older adults show decreased excitability of intracortical inhibitory circuits within the motor cortex at rest (Peinemann et al., 2001). SICI was significantly reduced in the older adult group compared to the young adults. The researchers hypothesized that the age-related decline in intracortical inhibition could be a result of decreased inhibitory interneuron excitability or an increase in facilitatory interneuron excitability, or a combination of both. This finding is further supported in task-dependent studies

which show that older adults have reduced ability to modulate intracortical inhibitory function compared to young adults (Talelli et al., 2008b; Fujiyama et al., 2009).

It was also found that older adults had reduced TCI compared to younger adults as indexed by iSP characteristics (Davidson & Tremblay, 2013). Additionally, young adults were shown to have greater hemispheric asymmetry, whereas the difference in inhibition between hemispheres in older adults was marginal (Davidson & Tremblay, 2013). The age-related changes in interhemispheric inhibition presented can be explained by the hemispheric asymmetry reduction in older adults (HAROLD) model (Cabeza, 2002). This model suggests that as we age, there is increased bilateral recruitment of functional activity in tasks for which one hemisphere is typically more dominant (McGregor et al., 2011). Reduced interhemispheric suppression in older adults is thought to be due to compensatory recruitment of the ipsilateral motor areas (McGregor et al., 2011; Heuninckx et al., 2008).

Current evidence also supports the hypothesis that there is a shift from predominantly inhibitory to excitatory interhemispheric interactions as we age (Fling et al., 2011). Importantly, there are data to suggest that changes observed in TCI with age (i.e., reduced iSP duration and iSP area (McGregor et al., 2011; Davidson & Tremblay, 2013)), may be mitigated by physical activity (McGregor et al., 2011). McGregor and colleagues (2011) quantified TCI using iSP duration and found that amongst three groups (active elderly, sedentary elderly, and young adults), iSP duration was significantly reduced in the sedentary and active elderly groups versus the young adults. Importantly, the active elderly group had significantly longer iSP duration compared to the sedentary group indicating that physical activity mitigated some of the age-related reduction in iSP duration. This study, however, was based on self-report of physical

activity level. Therefore, more research utilizing exercise interventions are required to confirm the finding that physical activity and exercise can mitigate the age-related reductions.

To study the age-related changes in neuroplasticity as a result of exercise, it is important to consider what defines an older adult. Currently, there is no standardized age range for the older adult population in research pertaining to neuroplasticity. Previous work utilizing TMS to quantify cortical and interhemispheric interactions in older adults have utilized various age ranges and means: from 48 to 71 with a mean age of 51 (Peinemann et al., 2001) to a smaller age range of between 60 to 85 years (McGregor et al., 2011) to group mean ages of 61.1 (Coppi et al., 2014) and 73.0 (Davidson & Tremblay, 2013). Meanwhile, research into the effects of acute exercise on cognition and behaviour in older adults have also used similar ranges. For example, one study investigating cognitive performance after an acute bout of exercise in older adults recruited participants between ages 60 and 90, with a mean age of 69.48 (Barella et al., 2010). Other work on cognitive function after acute aerobic exercise in older adults had a participant age range of 60 to 74 with a mean age of 65.5 (Kamijo et al., 2009). Given the wide range of ages that have been previously considered for the current study, we recruited participants between the ages of 50 and 90 to provide a representative population.

As we were interested in studying the effects of an acute bout of high intensity exercise on neuroplasticity in an aging population, many of the techniques reviewed here were employed. The exercise intervention employed a high intensity interval model. In particular, we carried out the current study using TMS to quantify corticospinal excitability using MEP recruitment curves and transcallosal inhibition indexed by iSP (see **section 1.2**) to better understand how exercise may impact age-related changes in neuroplasticity.

1.2 Research question, aims, and hypotheses

Research question: What is the impact of an acute bout of high intensity exercise on neuroplasticity in healthy older adults?

Aim 1: To determine the effects of an acute bout of high intensity exercise on corticospinal excitability in healthy older adults.

Hypothesis 1: Corticospinal excitability as measured by area under the MEP recruitment curve will increase after an acute bout of high intensity exercise in healthy older adults.

Aim 2: To determine the effects of an acute bout of high intensity exercise on interhemispheric interactions in healthy older adults.

Hypothesis 2: Transcallosal inhibition indexed by iSP area will increase after an acute bout of high intensity exercise in healthy older adults.

1.3 Significance

Given previous evidence showing that single bouts of aerobic exercise changes excitability in multiple intracortical and interhemispheric circuits, it may be that aerobic exercise can stimulate an environment that is optimized for induction of neuroplasticity. The current research will enhance our knowledge of how exercise affects the brain in older adults, the age at which many neurodegenerative disorders onset. The present research will provide insight into

how exercise could be used to mitigate age related changes in the brain as well as whether exercise therapies could be employed in association with rehabilitation in clinical populations.

Chapter 2: Methods

The present study was approved by University of British Columbia's Clinical Research Ethics Board (certificate #H16-01945). All participants provided written and verbal informed consent, in accordance with the principles of the Declaration of Helsinki.

2.1 Participants

Forty-one healthy older adult participants were recruited from the Greater Vancouver area. A computer program was used to pseudo-randomize these participants into either exercise or rest groups after accounting for age and sex. The result was that twenty-one were randomized into

the exercise group (8 males, mean age = 66.8 years old), and twenty were randomized into the rest group (5 males, mean age = 65.77 years old). Both left- and right-hand dominant individuals were included in the study. Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971; Appendix A). Participants were excluded if they had a history of any neurological disorder, including dementia, stroke, multiple sclerosis, Parkinson's, traumatic brain injury, psychiatric disorders, and substance abuse. Participants were also excluded if they had any contraindications to TMS, assessed by the TMS Screening Questionnaire (Appendix B). Participants were also screened with a cardiology supervised stress test to ensure they were safe to exercise prior to enrollment in the study. See **Table 2-1**.

Participant ID	Sex	Age	Group
HO01	F	56.6	Exercise
HO03	F	63.6	Exercise
HO05	F	64.7	Exercise
HO07	M	74.7	Rest
HO08	M	51.6	Exercise
HO09	M	85.5	Exercise
HO10	F	60.6	Rest
HO11	F	70.4	Rest
HO12	F	74.3	Exercise
HO13	F	68.1	Exercise
HO15	F	67.6	Rest
HO16	F	76.3	Exercise
HO17	M	61.4	Exercise
HO18	F	62.9	Rest
HO19	F	58.3	Rest
HO20	F	69.1	Rest
HO22	F	76.3	Exercise
HO23	F	67.7	Rest
HO24	F	63.6	Exercise
HO25	F	63.5	Rest
HO26	F	73.7	Rest
HO27	F	63.0	Exercise
HO28	M	67.9	Rest
HO29	F	73.6	Exercise
HO30	M	62.0	Exercise
HO31	M	59.0	Exercise

HO34	F	51.4	Exercise
HO36	M	65.5	Rest
HO37	F	62.9	Exercise
HO40	F	61.4	Rest
HO41	M	66.8	Rest
HO42	F	77.5	Rest
HO43	M	72.0	Exercise
HO44	F	71.1	Rest
HO45	F	57.5	Rest
HO46	M	52.9	Rest
HO47	M	77.2	Exercise
HO48	F	58.3	Rest
HO49	M	63.4	Exercise
HO50	F	68.0	Rest
HO51	F	76.3	Exercise

Table 2-1. Participant characteristics including sex and age.

2.2 Experimental Design

During the initial visit, participants provided informed consent, completed the screening forms, handedness inventory and cardiac screening. As these data were collected as a part of a larger clinical trial on day 2 we acquired a magnetic resonance imaging (MRI) scan of their brain. While the MRI data are not a part of this thesis, the T1 anatomical scan was used for stereotaxic registration during TMS sessions. Upon arrival on the third visit, we administered a baseline TMS assessment (see TMS measures section). Next, participants in the exercise group completed an acute bout of high intensity interval exercise for 23 minutes (see Exercise Protocol section); participants in the rest group sat for the same time while watching a nature documentary (see Rest Protocol section). Immediately after the exercise or rest, we administered a second TMS assessment to re-collect the same measures. A third TMS assessment was administered 30 minutes after the completion of exercise or rest. See **Figure 2-1**.

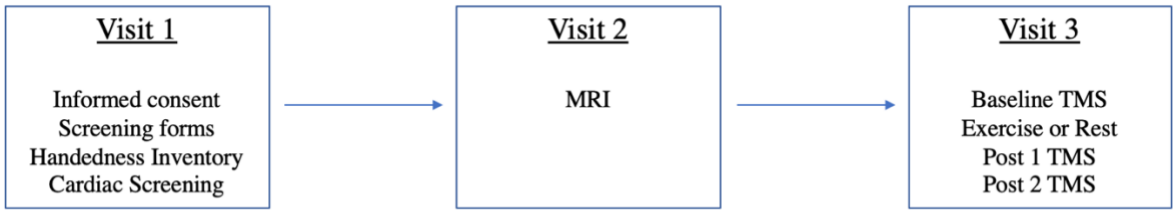


Figure 2-1. Experimental design.

2.3 Equipment

Exercise Bike

Participants in the exercise group completed a bout of high intensity aerobic interval exercise on a stationary recumbent bicycle (SciFit) for a total of 23 minutes. The participant's feet were secured used two Velcro straps and the seat distance and height were adjusted for each participant, so that the knee was flexed approximately between 25-45° during full leg extension and that the participant was comfortable during cycling. See **Figure 2-2**.

Figure 2-2. SciFit recumbent bike (FitnessZone, n.d.)

TMS

TMS was delivered over M1 using a 70-mm-diameter figure-of-eight coil (Bistim^2 Stimulator, Magstim). The optimal scalp location over M1 for stimulation to active the muscles to be recorded by EMG was saved onto each individuals T1 anatomic scan using a neuronavigation system (Brainsight, http://www.Rogue-Research.com). This ensured reliability of stimulation delivery location across the 3 TMS data collection sessions. During TMS the figure-of-eight coil was held over the "hand knob" area of the scalp at a 45 degree angle to stimulate in the posterior-anterior direction, as perpendicular to the precentral gyrus as possible (Rossini et al., 1994).

EMG Recordings

Surface electromyography electrodes (1 cm x 1 cm Kendall^{TM} Ag^+/AgCl Foam Electrodes with Conductive Adhesive Hydrogel, Covidien^{TM}, Mansfield, MA, USA) were used to measure the response to TMS. Participants sat comfortably in a chair with both arms resting on a pillow. Prior to application of the electrodes, mild abrasive gel and isopropyl alcohol was used on the skin to clean the area to reduce impedance. The primary active and reference electrodes were placed on the extensor carpi radialis (ECR) muscle in bipolar configuration, while the ground electrode was placed on the back of the hand. 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 were collected using LabChart Software (LabChart 7.0, AD Instruments Inc., Colorado Springs, CO).

2.4 Exercise Protocol

Cardiac Stress Test

To ensure participants were medically safe to partake in the exercise intervention and to individualize the intensity of exercise sessions, participants underwent a cardiologist supervised maximal exercise stress test. Prior to the stress test, participants were instructed to refrain from vigorous physical activity for 24 hours and to not eat a large meal within the 2 hour period leading up to the test. Upon arrival, participants' supine resting heart rate and blood pressure were recorded. Then, participants were seated on a stationary recumbent bicycle (SciFit). Heart rate and blood pressure were constantly monitored every 1 and 2 minutes respectively throughout the test. The test began at an initial wattage of 10 Watts for 2 minutes of warm-up. At every minute thereafter, the wattage was increased by 5, 10, or 15, depending on participant heart rate, blood pressure, and rate of perceived exertion (RPE) (Eng et al., 2004). Participants were asked to pedal between 50 and 80 revolutions per minute (RPM). The stress test was terminated when the participant stopped pedaling or when RPM dropped below 50 and continued to decline for more than 5 seconds. Participants cooled down between 2 and 3 minutes at 10 Watts and then laid down until heart rate and blood pressure returned to baseline.

Acute Bout of High Intensity Exercise

Participants in the exercise group completed a bout of high intensity aerobic interval exercise on a stationary recumbent bicycle (SciFit) for a total of 23 minutes. The session began with a warm-up, which consisted of cycling at 10 Watts for 5 minutes. Following warm-up, three repetitions of 3-minute high intensity bouts of exercise (75% of their max power output as determined from their cardiac stress test) which were interspersed with 3-minute bouts of active recovery (at 10 Watts) (Mang et al., 2014). During the high intensity intervals, participants were

instructed to sustain between 50 and 80 RPM. Heart rate was monitored using a Mio Alpha 53p heart rate monitor, and blood pressure was taken during the high intensity intervals to ensure they were in a safe range to continue the bout of exercise.

2.5 Rest Protocol

Participants assigned to the rest group sat for a total of 23 minutes. To maintain attention and prevent sleepiness during this time they watched a nature documentary ("Oceans" from the Planet Earth series). Heart rate was monitored during this session following the same schedule as during the exercise. These measures both standardized experimental conditions and ensured that the participant was at rest.

2.6 TMS Measures

To assess M1 excitability, the figure-of-eight coil was placed over the scalp over the hand representation in the hemisphere contralateral to the hand being recorded to evoke a muscle response of the ECR for both hemispheres. RMT was determined as the lowest stimulation intensity to evoke MEPs of at least 50 μV in 5 out of 10 consecutive trials (Rothwell et al., 1999). Once the hotpot was found it was marked on the neuronavigation system to ensure stimulation at the same site for every pulse. This procedure was repeated for both hemispheres.

Corticospinal Excitability

After RMT was established, thirty single-pulse trials were collected to obtain a MEP recruitment curve; ten at 100%RMT, ten at 130%RMT, and ten at 150%RMT (Mang et al., 2014). The MEP recruitment curve is a reliable way of quantifying corticospinal excitability (Wassermann et al., 1998). The order of stimulation intensity was randomized at each TMS assessment timepoint and for each hemisphere to prevent anticipation or order effects (Genschow

et al., 2018). For participants with very high RMTs (n = 2), 130%RMT and 150%RMT exceeded the maximum stimulator output of 100% maximum stimulator output (MSO). In those cases, 100%MSO was used as the stimulation intensity for all thirty pulses.

Transcallosal Inhibition

The ipsilateral silent period (iSP) is a measure of transcallosal inhibition (Chen et al., 2003). For this measure, participants were instructed to maximally squeeze a dynamometer for 5 seconds to activate the ECR muscle; this was determined to be their max voluntary contraction (MVC). Participants were then asked to maintain a grip of 50% of their MVC while keeping the other arm relaxed (Mang et al., 2015). Participants received visual feedback regarding grip strength via LabChart dynamometer and software that displayed force on a laptop screen placed directly in front of the individual. While the participant was squeezing the dynamometer to 50% MVC, ten single-pulses were delivered at 150% RMT over the ipsilateral hemisphere of the hand squeezing. Ipsilateral silent period was collected for both hemispheres. During the collection of these data, EMG activity was constantly monitored through the LabChart software. If the resting arm was not fully relaxed, or the participant was unable to maintain 50% of their MVC due to fatigue, short periods of rest were given. The iSP area was chosen for the primary index of TCI in the current study.

2.7 Data Processing

TMS measures were extracted from EMG data for the ECR muscle bilaterally for each dependent measure.

Corticospinal Excitability

Corticospinal excitability was quantified by calculating the area under the MEP recruitment curve for each participant (Wassermann et al., 1998). Custom MATLAB (Mathworks, Natick, NA) scripts were used to process and quantify peak-to-peak amplitudes of MEPs (μV). Ten MEPs at each stimulation intensity were collected from each hemisphere at each timepoint. The peak-to-peak amplitudes were averaged for each stimulation intensity. The three averaged values were then used to calculate the "area under the recruitment curve" (AUC; Singh et al., 2014b; **Figure 2-3**) using the equation:

$$\frac{100\%\ RMT\ (\mu V)}{2} + \frac{100\%\ RMT\ (\mu V) + 130\%\ RMT\ (\mu V)}{2} + \frac{130\%\ RMT\ (\mu V) + 150\%\ RMT(\mu V)}{2} + \frac{150\%\ RMT\ (\mu V)}{2}$$

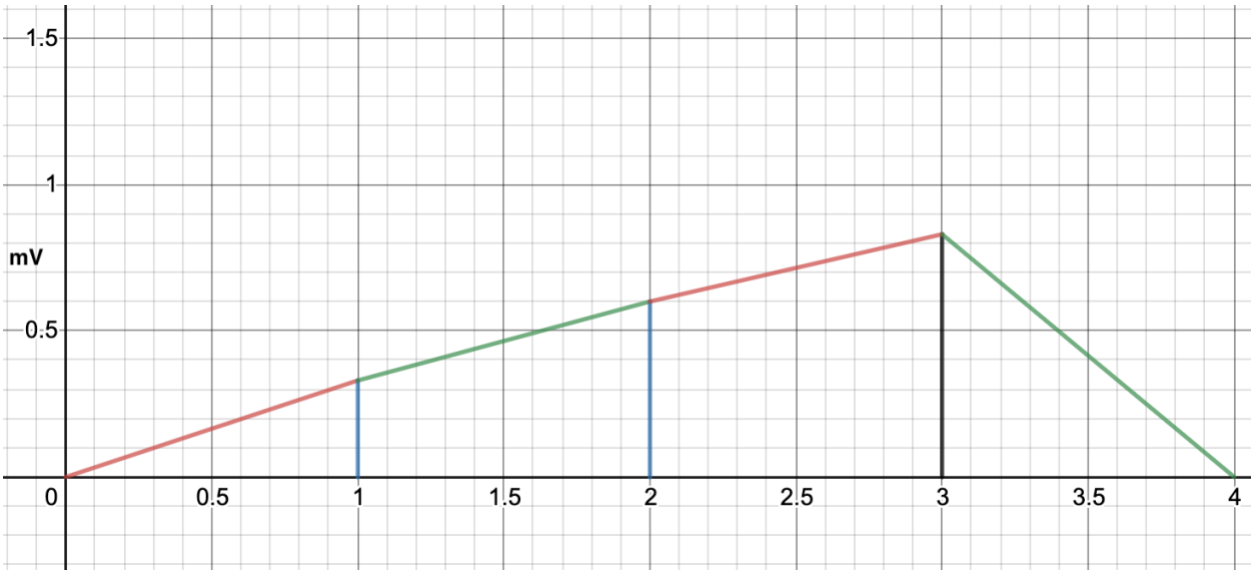


Figure 2-3. Area under the MEP recruitment curve.
Visualization of the area under the MEP recruitment curve. Data points were taken from a representative participant.

Transcallosal Inhibition

Transcallosal inhibition was indexed by iSP area. Custom MATLAB (Mathworks, Natick, NA) scripts were used to process and quantify iSP area in μV * s (Kuo et al., 2017; Neva et al., 2017). The iSP area was calculated as the area under the rectified EMG data between the

onset and offset of the iSP (**Figure 2-4**); the onset is defined as the point where the rectified EMG signal drops below the pre-stimulus muscle activity, while the offset is when the EMG signal returns to the pre-stimulus mean (Davidson & Tremblay, 2013). A larger value indicates an increase in inhibition from the contralateral hemisphere.

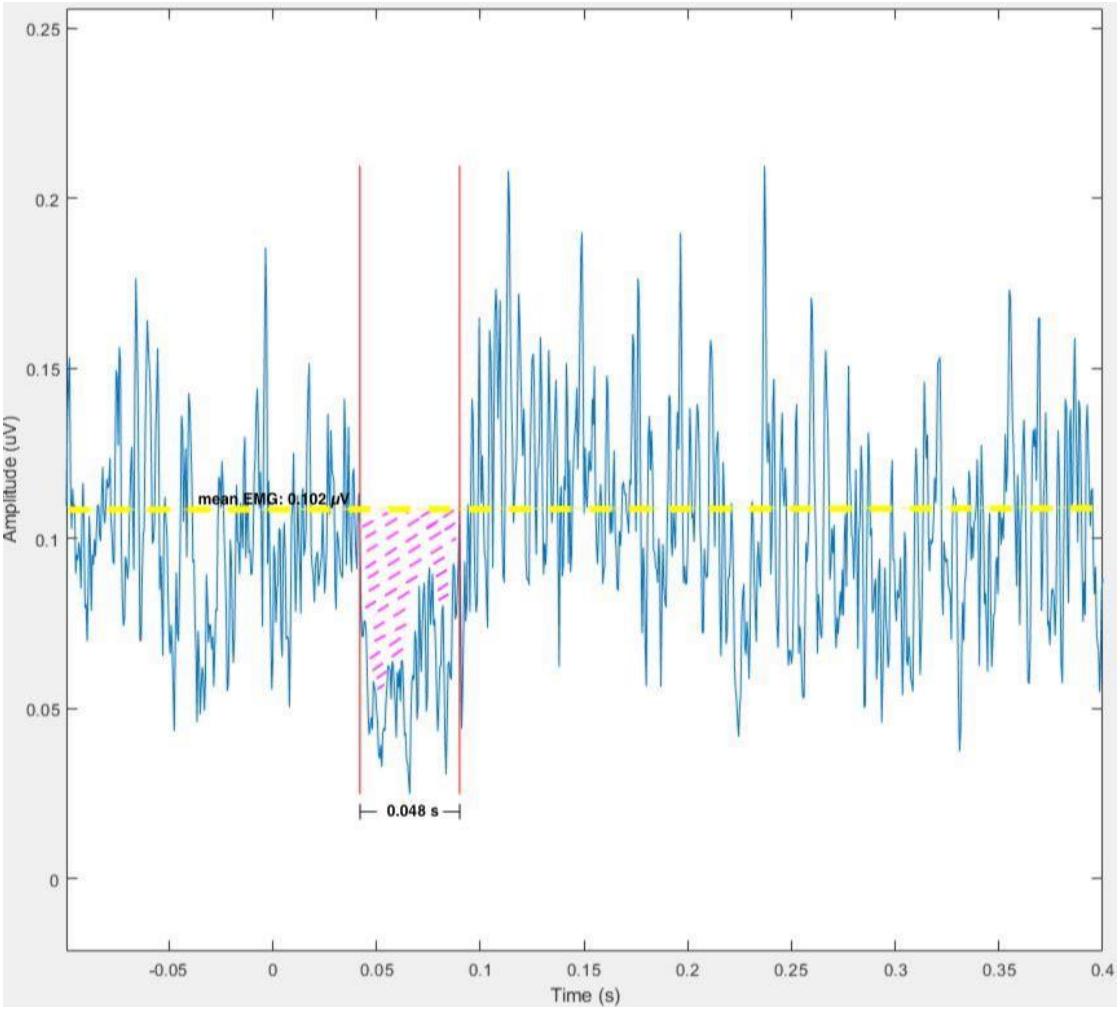


Figure 2-4. Quantifying iSP area.
Visualization of the iSP area (in purple). The yellow dotted line indicates the pre-stimulus EMG, in μV. The two red vertical lines indicate the onset and offset of the iSP, with the duration being 0.048s in this example. Data shown was taken from a representative participant

2.8 Statistical Analysis

Statistical procedures were conducted using SPSS (SPSS 26.0) software. All assumptions for performing ANOVA were met, including independence of individual observations, normality, and homogeneity. Significance level for all analyses was set at $p < 0.05$.

Exploratory Analyses on Sex and Age

To investigate sex differences between the measures of interest, independent samples t-tests were conducted for participants' baseline area under the MEP recruitment curve and iSP area.

To investigate age's influence on area under the MEP recruitment curve and iSP area, Pearson's correlations were conducted on age and each dependent variable in both hemispheres for both exercise and rest groups at each timepoint.

Between Group Comparisons

To ensure that the two groups (exercise and rest) were comparable, independent samples t-tests were conducted for participants' age.

To confirm that baseline measures of the two dependent variables: corticospinal excitability, and iSP area were not significantly different between the exercise group ($n = 21$) and the rest group ($n = 20$), independent samples t-tests was performed on each variable area for both hemispheres.

Corticospinal Excitability

Hypothesis 1: Corticospinal excitability (measured as area under the MEP recruitment curve) will increase after an acute bout of high intensity exercise in healthy older adults.

To test hypothesis 1, a mixed design ANOVA was conducted to determine if corticospinal excitability was affected by exercise. The dependent variable was the area under the recruitment curve. The between group factor was GROUP (exercise, rest), and the within group factors were: TIMEPOINT (baseline, post 1, post 2) and HEMISPHERE (dominant, non-dominant).

Transcallosal Inhibition

Hypothesis 2: Transcallosal inhibition indexed by iSP area will increase after an acute bout of high intensity exercise in healthy older adults.

Hypothesis 2 was tested by conducting a mixed design ANOVA to determine if iSP area was affected by exercise. The between group factor was GROUP (exercise, rest), and the within group factors were: TIMEPOINT (baseline, post 1, post 2) and HEMISPHERE (dominant, non-dominant).

Chapter 3: Results

3.1 Exploratory Analyses on Sex and Age

Independent samples t-tests were conducted on the two main dependent variables of the current experiment to uncover any sex differences. Males had significantly greater iSP area in both hemispheres at baseline while there were no differences between sex for area under the MEP recruitment curve (**Table 3-1)**.

	Male	*Female*	*SE Mean Difference*	*t*
Area Under MEP Recruitment Curve				
Dominant Hemisphere	1.423	1.505	0.275	0.279
Non-Dominant Hemisphere	1.379	1.457	0.242	0.322
iSP Area (µV * s)				
Dominant Hemisphere	0.00283	0.00130	0.00049	**-3.107
Non-Dominant Hemisphere	0.00287	0.00132	0.00058	*-2.686

Table 3-1. Baseline means of two dependent variables based on sex.
Baseline means of two dependent variables: Area under the MEP recruitment curve and iSP area. Independent samples t-tests revealed sex differences in iSP area at baseline in both hemispheres but not for area under the MEP recruitment curve. Note: *$p < .05$, ** $p < .01$, *** $p < .001$.

Exploratory analyses were also conducted on age. Pearson's correlations were conducted to explore the relationship between age and both dependent variables: area under the MEP recruitment curve and iSP area for both hemispheres and both exercise and rest groups. Results showed no significant correlations, $p > .05$. See **Figures 3-1** and **3-2**.

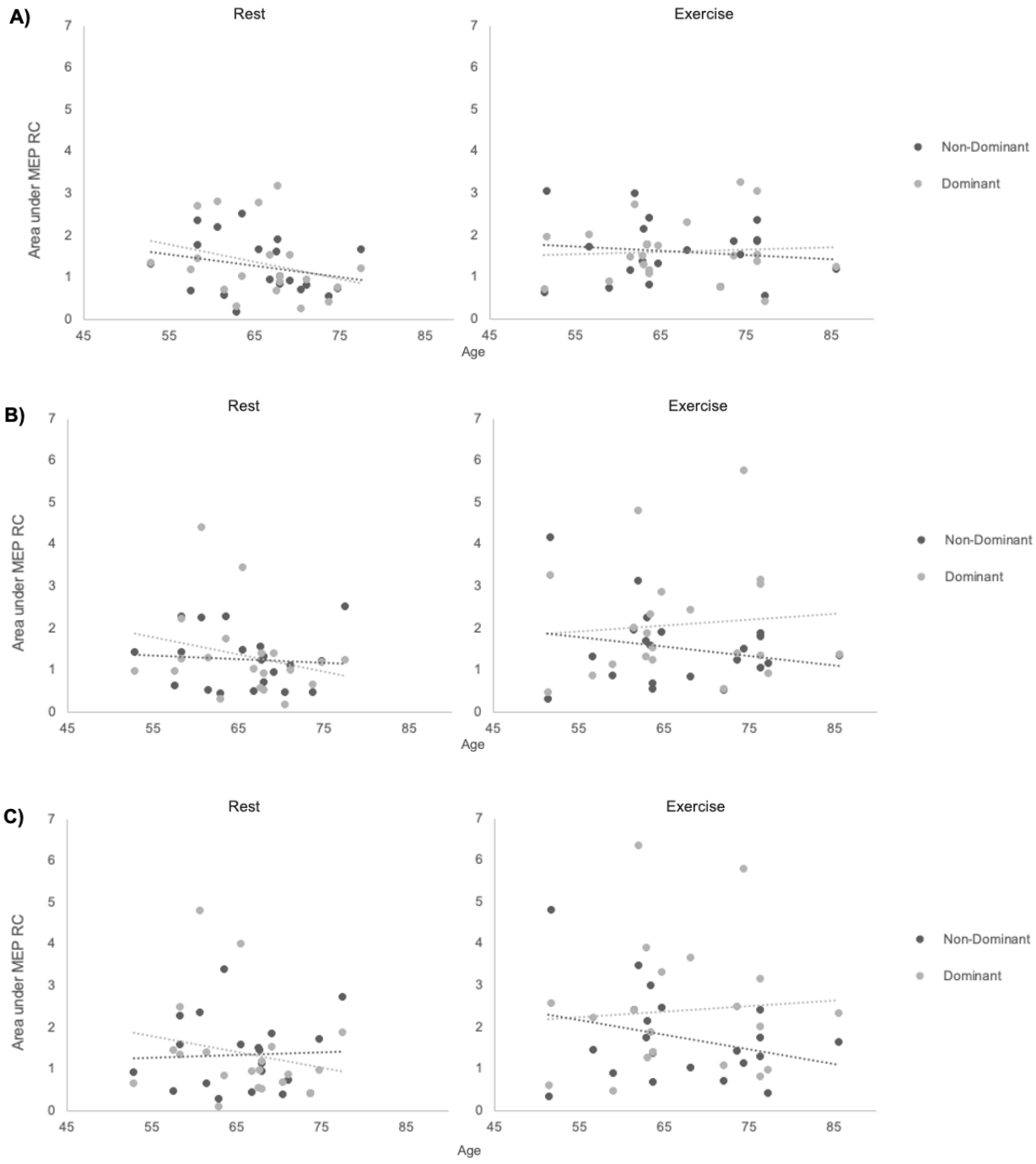


Figure 3-1. Scatterplots of age and area under the MEP recruitment curve.
The Y-axis denotes Area under the MEP recruitment curve. The X-axis denotes age. Scatterplots show the relationship between the two variables at (A) baseline, (B) Post 1, and (C) Post 2.

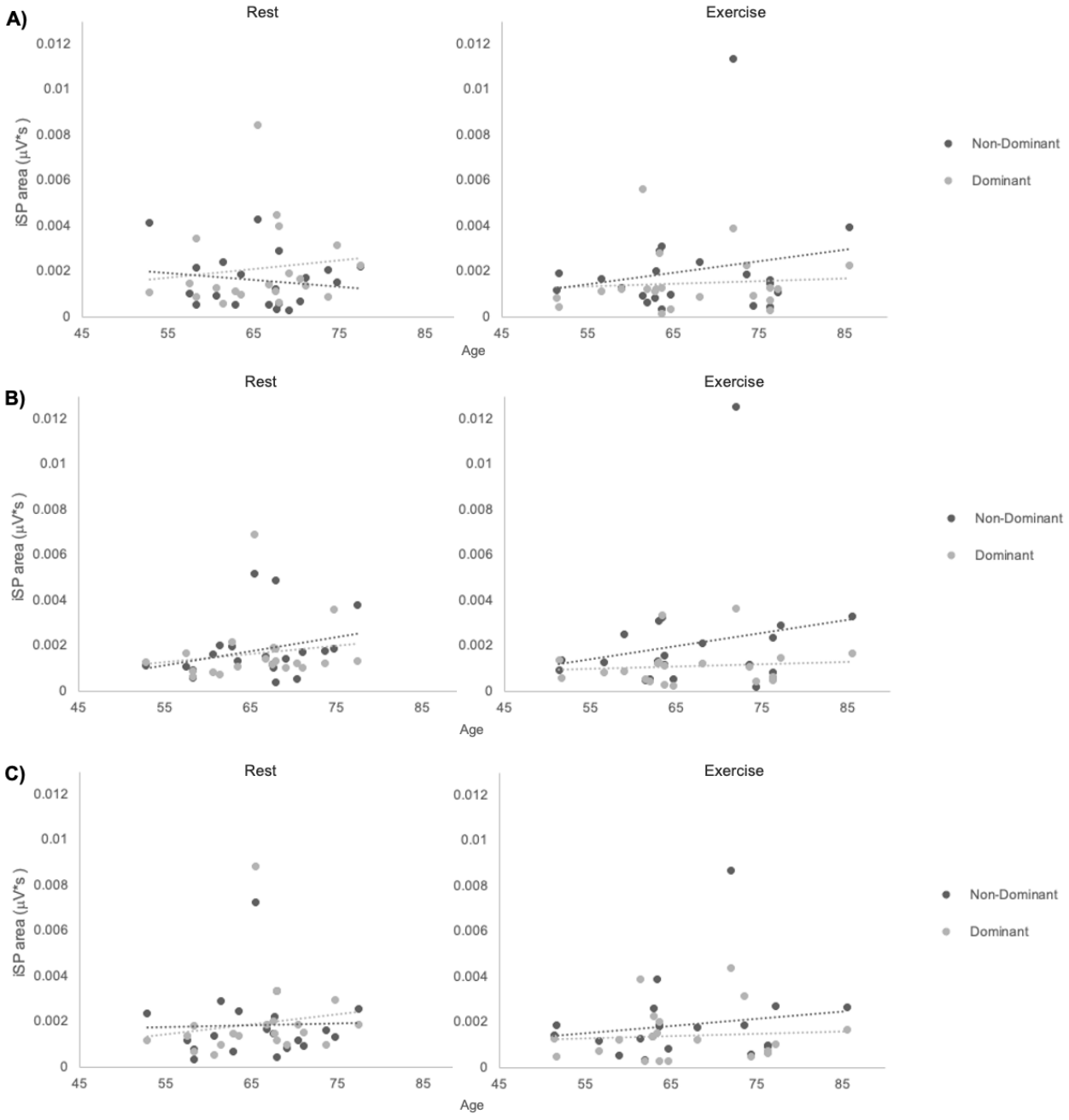


Figure 3-2. Scatterplots of age and iSP area.
The Y-axis denotes iSP area. The X-axis denotes age. Scatterplots show the relationship between the two variables at (A) baseline, (B) Post 1, and (C) Post 2.

3.2 Between Group Comparisons

To ensure that the two groups (exercise and rest) were comparable, independent samples t-tests were conducted on participants' age and the two main dependent variables of the current experiment. The two dependent variables: Area under the MEP RC and iSP area did not differ significantly between groups at baseline, nor did participant age (**Table 3-2)**.

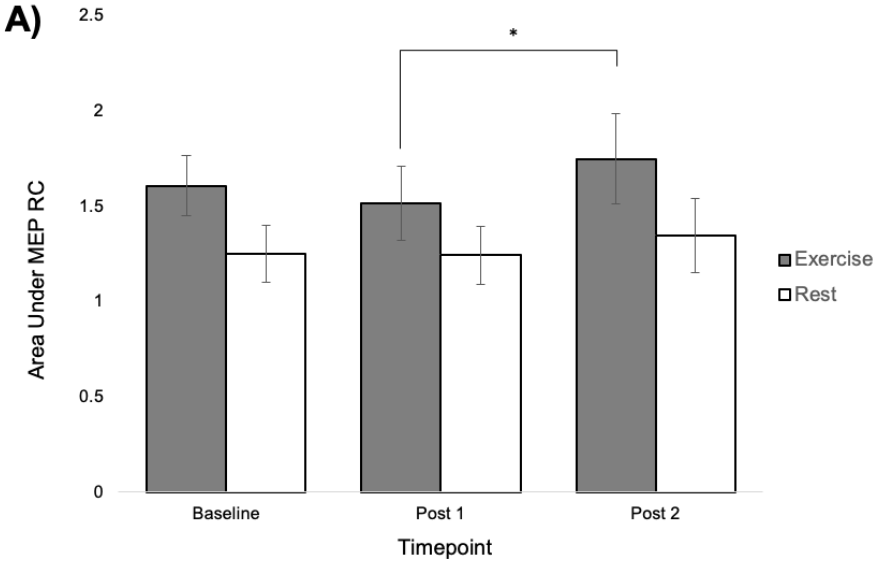
	Exercise Group	*Rest Group*	*SE Mean Difference*	*t*
Area Under MEP Recruitment Curve				
Dominant Hemisphere	1.613	1.342	0.253	1.072
Non-Dominant Hemisphere	1.606	1.250	0.218	1.632
iSP Area (μV * s)				
Dominant Hemisphere	0.0015	0.0021	0.0005	-1.255
Non-Dominant Hemisphere	0.0020	0.0016	0.0005	0.731
Age (years)				
	66.80	65.77	2.438	0.422

Table 3-2. Baseline means of participant age and two dependent variables based on group. Baseline means of participant age and two dependent variables: Area under the MEP recruitment curve and iSP area. Independent samples t-tests revealed the two groups (exercise and rest) were not significantly different at baseline. Note: *$p < .05$, ** $p < .01$, *** $p < .001$.

3.3 Corticospinal Excitability

Corticospinal excitability was quantified using the Area under the MEP recruitment curve. A greater value indicates higher corticospinal excitability. A mixed design ANOVA was conducted with between group factor GROUP (exercise, rest), and within group factors: TIMEPOINT (baseline, post 1, post 2) and HEMISPHERE (dominant, non-dominant). The

analysis revealed a main effect of timepoint ($F(1.512, 58.96)= 5.049$, $p= .016$) but no main effect of hemisphere or group, although between group difference trended towards significance ($F(1, 39)= 3.941$, $p= .054$). There was a 3-way Group by Timepoint by Hemisphere interaction effect ($F(2, 78)= 3.488$, $p= .035$). Post-hoc comparisons adjusted for multiple comparisons using the Bonferroni correction revealed a group difference in the dominant hemisphere at timepoint Post 2 ($p= .027$). There was also a simple main effect of timepoint in the Exercise group. In the non-dominant hemisphere, Area under the MEP recruitment curve was greater at both Post 1 ($p= .023$) and Post 2 ($p= .003$) compared to Baseline, but there was no difference between Post 1 and Post 2. Whereas in the dominant hemisphere, Area under the MEP recruitment curve was greater at timepoint Post 2 compared to Post 1 ($p= .038$; **Figure 3-3)**.



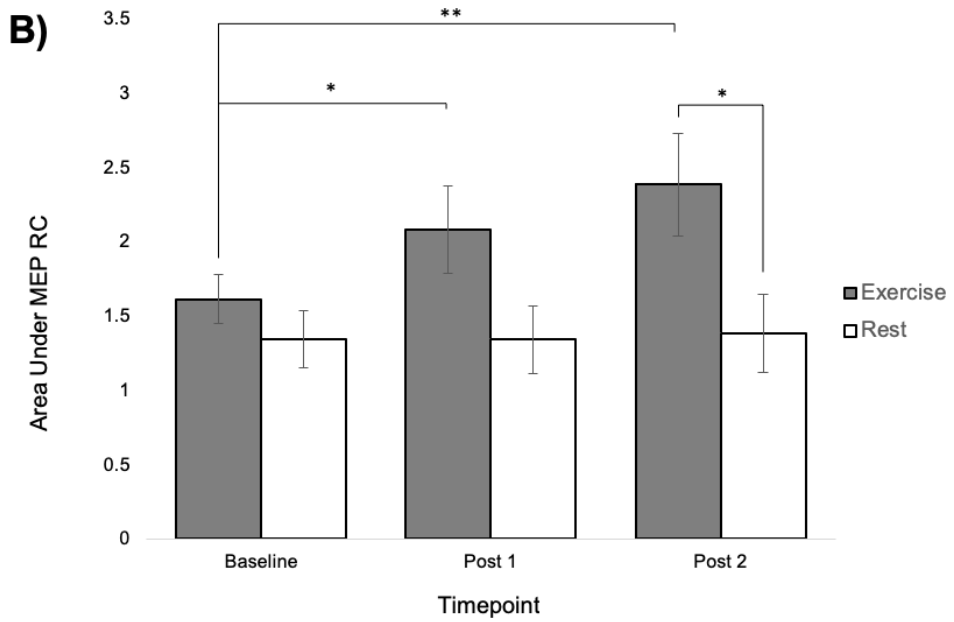


Figure 3-3. Area under the MEP recruitment curve changes across timepoints in the exercise group in both hemispheres.
The Y-axis denotes Area Under the MEP RC. Grey bars indicate data from the Exercise group and white bars indicate data from the Rest group. In the non-dominant hemisphere (A), Area under the MEP RC was significantly greater at timepoint Post 2 in the exercise group. In the dominant hemisphere (B), baseline values were significantly lower than both Post 1 and Post 2 timepoints; there was also a between group difference at timepoint Post 2. Error bars represent SEM. Note: *$p < .05$, ** $p < .01$.

3.4 Transcallosal Inhibition

iSP Area

A mixed design ANOVA was performed with between group factor GROUP (exercise, rest), and within group factors: TIMEPOINT (baseline, post 1, post 2) and HEMISPHERE (dominant, non-dominant) to determine changes in iSP area. There was no main effect of group ($F(1, 39)= .119$, $p= .732$), timepoint ($F(2, 78)= .933$, $p= .398$), or hemisphere ($F(1, 39)= 1.407$, $p= .243$). However, there was an interaction effect between timepoint and hemisphere ($F(2, 78)= 3.211$, $p= .046$) (**Figure 3-4**).

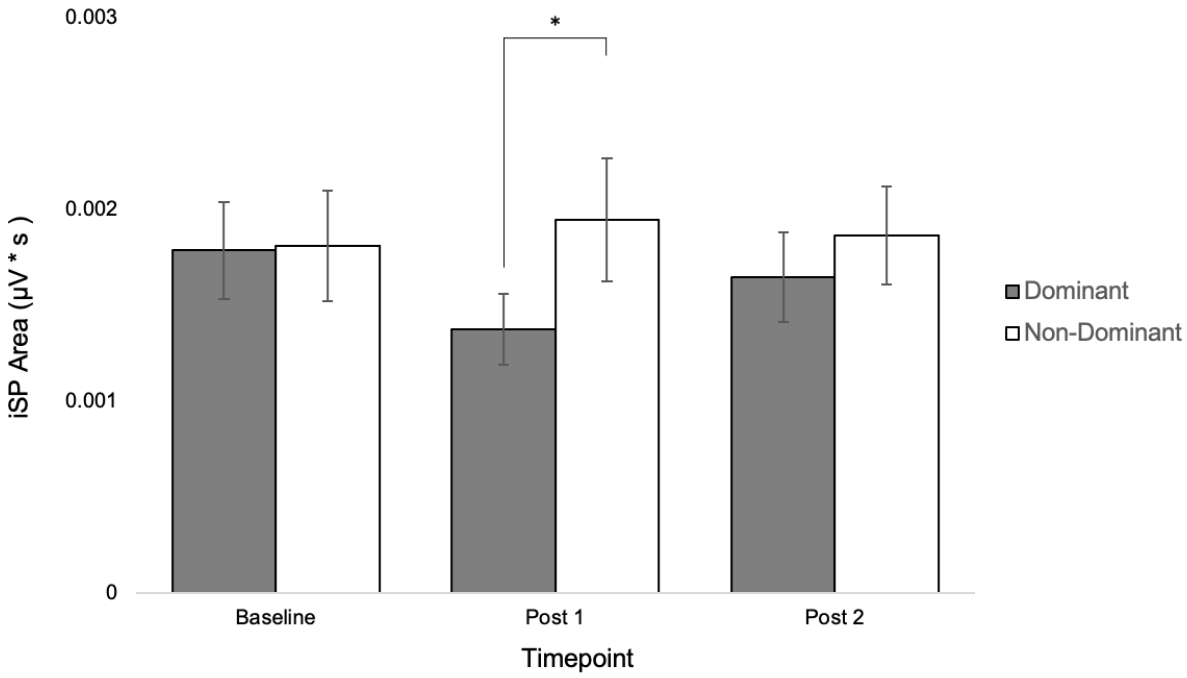


Figure 3-4. Interaction between hemisphere and timepoint at timepoint Post 1.
The Y-axis denotes iSP area (μV*s). Grey bars indicate data from the Dominant hemisphere and white bars indicate data from the Non-Dominant hemisphere. Error bars represent SEM. Note: *$p < .05$, ** $p < .01$.

Supplementary post-hoc analyses using Bonferroni correction revealed that this interaction effect was driven by hemispheric differences within the Exercise group at timepoint Post 1; iSP area was significantly greater in the non-dominant compared to the dominant hemisphere (p= .008). As a larger value in iSP area indicates an increase in inhibition from the contralateral hemisphere, these results infer that at the Post 1 timepoint, the non-dominant hemisphere increased inhibition whereas the dominant hemisphere decreased inhibition (**Figure 3-5)**.

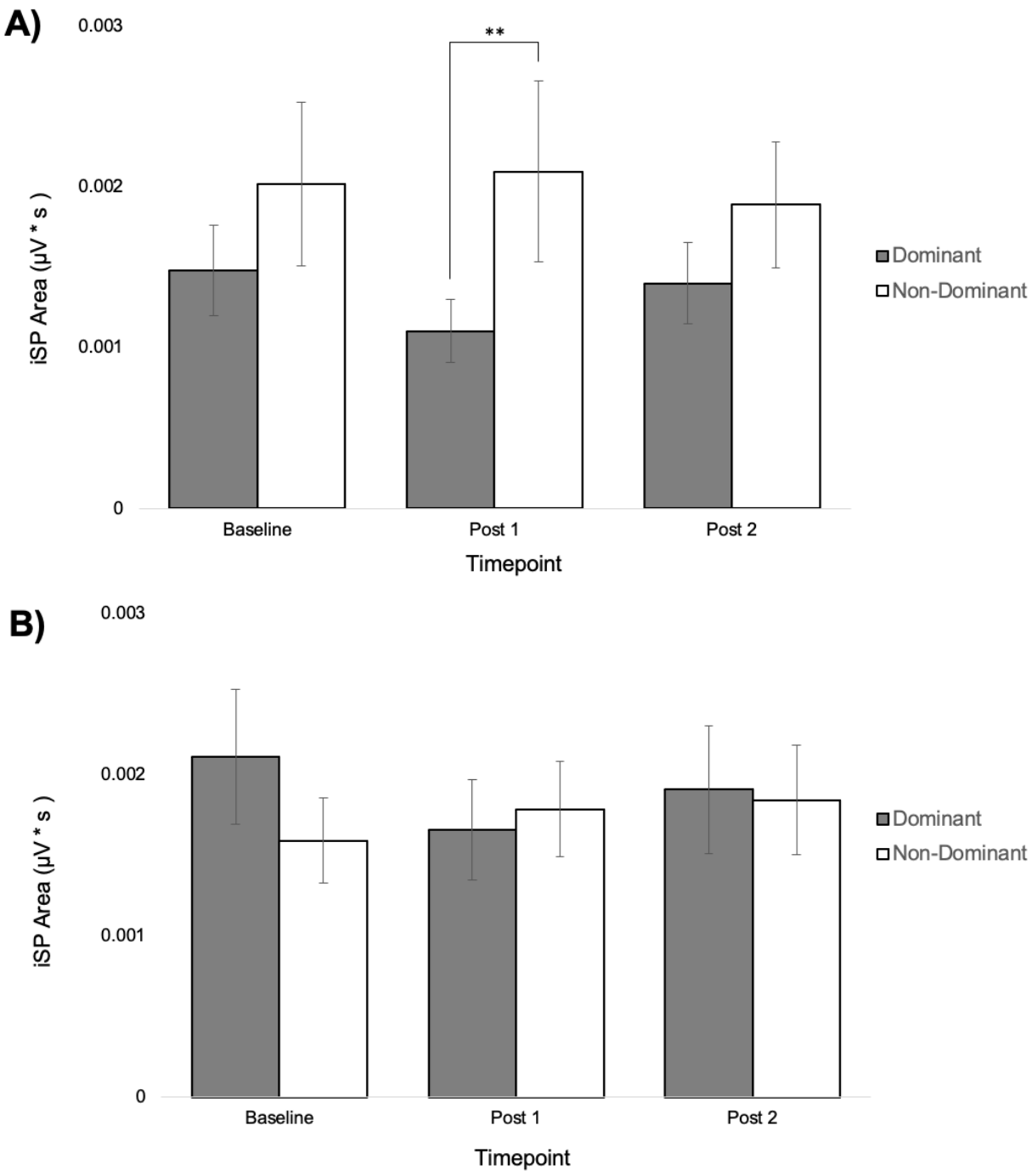


Figure 3-5. Hemispheric differences in iSP area shown in the Exercise group immediately post exercise.

The Y-axis denotes iSP area (μV*s). Grey bars indicate data from the Dominant hemisphere and white bars indicate data from the Non-Dominant hemisphere. In the Exercise group (A), iSP area is significantly greater in the non-dominant hemisphere compared to the dominant hemisphere at timepoint Post 1. In the Rest group (B), there were no changes. Error bars represent SEM. Note: *$p < .05$, ** $p < .01$.

Chapter 4: Discussion

4.1 Aim 1: An acute bout of high intensity exercise increases corticospinal excitability in older adults

4.1.1 Increased corticospinal excitability and hemispheric difference in response to acute high intensity exercise

In the current thesis, we determined that an acute bout of high intensity exercise increases corticospinal excitability in healthy older adults. Similar research with healthy young adult participants also showed increased corticospinal excitability after high intensity exercise as induced by PAS (Mang et al., 2014). Other work reported no change in corticospinal excitability, but instead that intracortical relationships change after moderate and low intensity exercise (McDonnell et al., 2013; Smith et al., 2014, Singh et al., 2014a). Thus, it is possible that non-fatiguing exercise does not influence corticospinal excitability, whereas high intensity interval exercise does. Another possible explanation for the shift towards cortical changes observed with age comes from previous studies showing that older adults having reduced inhibitory function compared to young adults (Talelli et al., 2008b; Fujiyama et al., 2009). Inhibition at both cortical and spinal levels decreases with advancing age (Kossev et al., 2002; Peinemann et al., 2001; Sale & Semmler, 2005; Kido et al., 2004). As a consequence of reduced inhibitory processes, older adults have difficulty performing interlimb movements (Fujiyama et al., 2009). Together, data from the current thesis and previous literature suggest that with age there is a shift from inhibitory processes to excitatory processes, and also that there is potential for high intensity exercise to facilitate increases in corticospinal excitability.

Interestingly, changes in corticospinal excitability were more evident in the dominant hemisphere. In the non-dominant hemisphere, corticospinal excitability was not significantly different from baseline immediately following exercise, but was greater 30 minutes post exercise

compared to immediately after exercise. However, in the dominant hemisphere, there is a dramatic increase in corticospinal excitability both immediately and 30 minutes post exercise compared to baseline. This hemispheric difference in response could be a result of the right hemisphere experiencing greater age-related decline compared to the left (Dolcos et al., 2002; Coppi et al., 2014). In the current study, 38 out of 41 participants were right hand dominant and thus, left-hemisphere dominant. The lack of response in cortical excitability in the non-dominant hemisphere for majority of participants could be due to the right hemisphere experiencing greater decline compared to the left. It is possible that as we age, the use of our dominant side allows this hemisphere to be more resistant to age-related shifts (Coppi et al., 2014).

4.1.2 Neurochemical underpinnings of corticospinal excitation with age

Previous work has suggested that as we age, there is a shift towards excitatory processes in the brain (Fling et al., 2011). The shift from inhibitory to excitatory processes may be explained by magnetic resonance spectroscopy (MRS) studies, which have been used to study GABA concentration and activity in relation to aging (Mooney et al., 2017). It was concluded that while GABA concentration does not change with age, extrasynaptic $GABA_A$ activity may be reduced as a consequence of aging (Mooney et al., 2017). Hermans and colleagues (2018) also showed that GABA levels decrease with age in the cortico-subcortical network, specifically the pre- supplementary motor area, which plays a role in mediating motor inhibition. As GABA is primarily an inhibitory neurotransmitter, this may be a potential explanation for the lack of intracortical inhibition observed in this study. These results have implications for age-related conditions, such as stroke, since motor recovery is dependent on inhibitory processes in the brain.

The hypothesis that age-related reduction in inhibition is related to GABAergic activity is also supported by work using animal models. Rat models show that twelve weeks of aerobic exercise training can rescue aging related overactivity of the nervous system by improving the GABAergic system in the paraventricular nucleus (Li et al., 2017). Li and colleagues (2017) showed that dose of exercise is important to ameliorate the decline seen in the aging brain. Thus, it is possible that an acute bout of aerobic exercise, as conducted in the current study, may intensify the disinhibition, as the dose and repetition are not high enough. Further research should be conducted to investigate: 1) GABA related changes after an acute bout of exercise and 2) changes in corticospinal excitability after a longer, high frequency, exercise intervention program.

4.1.3 Exercise and its effects on functions modulated by neuroplasticity

Changes in neuroplasticity after exercise can have implications for cognitive and behavioural function in older adults. A review on aerobic exercise and its effects on cognitive function and neuroplasticity found that a period of 6 months of continuous moderate levels of aerobic activity is sufficient to improve cognitive function, specifically executive control (Erickson & Kramer, 2009). Altered brain activity and increases in grey matter volume seem to drive these improvements. While the current study was not longitudinal, results suggest that as little as one session of high intensity aerobic exercise alter cortical excitability. Previous research shows the importance of disinhibition in motor learning via long-term potentiation for promoting excitatory connections to M1 (Hess & Donoghue, 1994; Hess et al., 1996; Jones, 1993). A review noted that motor performance is greatly affected by age, due to the reduction of motor plasticity, however, the acquisition of new motor skill is relatively unaffected by age (Voelcker-Rehage, 2008). A subsequent review supported the finding that long-term high physical activity

enhances the initial phase of motor learning, however, in this work it was noted that there were no studies examining the influence of an acute bout of exercise (Hubner & Voelcker-Rehage, 2017). The current study provides evidence that an increase in cortical excitability is brought about by an acute session of high intensity interval exercise. This could serve as a starting point to promote neuroplastic changes that could lead to improving motor performance, by countering age related deterioration or slowing age-related disorders.

Taken together, data from the current study shows that an acute bout of high intensity aerobic exercise increases corticospinal excitability in older adults. These neuroplastic changes after a single bout of high intensity exercise may provide opportunities for cognitive and behavioural functions to improve, which may ultimately benefit the older adult population, as well as individuals with age-related onset disorders.

4.2 Aim 2: An acute bout of high intensity exercise influences transcallosal inhibition in older adults

4.2.1 Sex differences in TCI at baseline

Exploratory analyses of potential sex differences in baseline measures in the current experiment showed that males had significantly greater iSP area, and thus, a great degree of TCI, compared to females in both hemispheres. Previous work suggested that females have reduced cortical excitability (Kuo et al., 2006). This is thought to be a result of sex hormones such as progesterone which contributes to the reduction of cortical excitability in females with regular menstrual cycles (Kuo et al., 2006). However, there is lack of evidence suggesting the same in interhemispheric interactions. Also, Kuo and colleagues (2006) studied young adults whereas the current study's participants are older adults. To date, no other studies have investigated sex

differences in transcallosal inhibition in older adults. This issue should be investigated further in future work.

4.2.2 Hemispheric differences in TCI

In the current study, we showed that immediately after an acute bout of high intensity aerobic exercise, there was a hemispheric difference in transcallosal inhibition. The iSP area in the dominant hemisphere was reduced compared to the non-dominant hemisphere. This indicates that the dominant hemisphere decreased inhibition being placed on the non-dominant hemisphere, which allows the non-dominant hemisphere to increase inhibition placed on the dominant hemisphere (see **Figure 3-5**). The hemispheric difference observed disappeared 30 minutes post exercise, indicating that the changes were short lasting. A previous study showed that TCI decreased bilaterally after an acute session of lower limb exercise in healthy young adults (Neva et al., 2017). It is important to note that this previous study used moderate intensity exercise. Thus, it is possible that our novel finding was attributed to the use of high intensity interval training exercise. Nonetheless, our data suggests that as we age, the dominant hemisphere seems to follow the trend of decreased TCI post exercise in young adults, but this reduction of inhibition is not bilateral.

Previous work has studied hemispheric asymmetry and its relation to aging. The results in the current study can be explained by the HAROLD model (Cabeza, 2002), which hypothesizes that interhemispheric inhibition in older adults is reduced due to compensatory recruitment of the ipsilateral motor areas (McGregor et al., 2011; Heuninckx et al., 2008). Other work shows that the right hemisphere has a greater age-related decline compared to the left in right-handed individuals (Dolcos et al., 2002). Applying these models to interpret our current data, the dominant hemisphere, which was the left hemisphere in 38 out of 41 participants, may be

playing a compensatory role due to the age-related decline of the right hemisphere. As a result, an acute bout of exercise may promote the dominant hemisphere to disinhibit the opposite hemisphere, much like what was seen bilaterally in young adults (Neva et al., 2017). Future work should compare the effects of acute high intensity interval training exercise on transcallosal inhibition in young and older adults.

4.2.3 Neurophysiological underpinnings of changes in TCI

Unlike the neurological underpinnings of SICI, SCF, and LICI, which are understood to be GABA regulated, there is no consensus on the neural correlates that contribute to TCI. It is likely that TCI, just like measures of intracortical inhibition, is mediated by alterations in GABAergic-receptor functioning (Neva et al., 2017). GABAergic-receptor functioning seems to be implicated in many TMS measures (Ziemann et al., 1996; Chen et al., 2003). As GABA is a primary inhibitory neurotransmitter, coupled with evidence showing that intracortical inhibition interacts with TCI (Udupa et al., 2020; Daskalakis et al., 2002), it is likely that GABAergic function is also involved in modulating TCI. As mentioned in the previous section, aerobic exercise seems to improve GABAergic systems (Li et al., 2017). However, as GABA levels were not measured in the current study, future work should be undertaken to uncover the specific interneuronal relationships involved, including the contributions of neurotransmitters.

Early research identified that iSP is in part mediated by fibers passing through the corpus callosum due to the absence or delay of an iSP in individuals with damaged to their corpus callosum (Meyer et al., 1995, 1998). Other research has shown that young children who have not developed a fully functional corpus callosum also have no detectable iSP (Heinen et al, 1998). Diffusion tensor imaging (DTI) work showed that there is a significant fractional anisotropy (FA) decline in the genu of the corpus callosum with advancing age (Abe et al., 2002). More

recent work shows myelin in the corpus callosum, as measured by myelin water fraction (MWF), decreases with age as well (Lynn et al., 2020). Additionally, earlier magnetic resonance imaging research also concluded that the size of the corpus callosum declines with age in healthy individuals (Janowsky et al., 1996). This age-related deficit seen in the corpus callosum could be impacting baseline levels of TCI, which may be mitigated by an acute bout of exercise in the dominant hemisphere, as shown by an increase in inhibition immediately post exercise.

Taken together, the current study shows that an acute bout of high intensity aerobic exercise results in an interaction effect between timepoint and hemisphere. The hemispheric difference observed may be explained by age-related hemispheric asymmetry. There is also a potential role of GABAergic systems in the modulation of TCI after exercise in older adults which could be investigated in future work.

Chapter 5: Conclusion

5.1 General Conclusions

The current study has increased our understanding of how high intensity exercise affects the brain in older adults and provides insight on how neurophysiological circuits are affected. Specifically, corticospinal and interhemispheric interactions in the brain respond differently to an acute bout of high intensity exercise. It was determined that an acute bout of high intensity exercise increased corticospinal excitability and influenced transcallosal inhibition in older adults. There also seems to be hemispheric differences in the way both cortical and interhemispheric interactions respond to high intensity exercise. Evidence from the current thesis distinguish high intensity from moderate or low intensity exercise and suggest that fatiguing high intensity exercise may be required to bring about specific neuroplastic changes in the brain. The results from this study may have clinical implications for prescribing exercise as an intervention in aging populations or those with age-related neurological disorders.

5.2 Limitations

The current study is not without limitations. The use of TMS in this study limits our understanding of the current neurophysiological circuits at play during these high intensity exercise induced changes. As our measures of corticospinal excitability and transcallosal inhibition are indexed by measures of muscle activity, it does not provide a complete picture of the neurochemical underpinnings of how and why those measures are changing. To overcome this limitation, future studies should utilize TMS in conjunction with other methods such as magnetic resonance spectroscopy which mapped metabolite concentrations in the brain and

would allow contextualization of both corticospinal and interhemispheric interactions on a large scale and provide insight into the neurochemical causes that lead to those changes.

Another limitation stems from the process of quantifying TCI. Our measure of iSP area is heavily dependent on the determination of onset and offset of the iSP. Thus, rater error can play a role in how the variable is quantified. However, previous studies have found that test-retest and inter-rater reliability of measuring iSP is high (Fleming & Newham, 2017). To account for this possible issue, future studies could use multiple raters to process TCI data to ensure that inter-rater reliability.

5.3 Future directions

In the current study, an acute bout of high intensity exercise increased corticospinal excitability and resulted in hemispheric differences in transcallosal inhibition. Much of the interpretation of data in the current study was based off of studies showing age related differences between older and younger adults. Future studies should directly compare measures of neuroplasticity after high intensity interval exercise in a young and older adult population. In addition, to investigate whether GABA plays a role in modulating TCI, two areas of research should be undertaken: 1) utilizing MRS to quantify GABA post exercise interventions and 2) quantifying TCI before and after ingesting GABA receptor agonist drugs in young and older adults. Lastly, as previous studies have shown the benefits of longer-term exercise protocols on cognitive and behavioural tasks modulated by cortical and interhemispheric excitability, future work should quantify changes in neuroplasticity following a multi-session exercise intervention.

5.4. Significance

In conclusion, the data from this study indicate that there are changes in excitability and interhemispheric interactions after an acute bout of high intensity exercise in an older adult population. In combination with previous research, my data show that it is like that exercise stimulates a neural environment that is conducive for neuroplasticity. The present findings contribute to a greater understanding of the benefits of using exercise to mitigate age-related disorders. Altogether, this work helps to illustrate the neurophysiological underpinnings of how exercise impacts the brain and provide support for the utilization of exercise therapies in clinical populations.

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Appendices

Appendix A: Edinburgh Handedness Inventory

Participant Code: _____

Please indicate with a check (✓) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put two checks (✓✓).

If you are indifferent, put one check in each column (✓ | ✓).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH – LH =	
Result	R = (D / CT) × 100 =	
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)		

Appendix B: 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.

_____
_____