

**MEASURING THE ACUTE EFFECTS OF TWO AEROBIC EXERCISE
TRAINING METHODS ON CORTICAL EXCITABILITY IN PEOPLE WITH
CHRONIC STROKE**

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Abstract

Background: Aerobic exercise (AE) upregulates neurotrophins and alters brain excitability post-stroke. Using transcranial magnetic stimulation (TMS) we compared the acute effects of moderate intensity continuous exercise (MICE) versus high intensity interval training (HIIT) on cortical excitability in patients with chronic stroke.

Methods: Participants completed 25 min MICE (60 % VO₂ max) and HIIT (80 % VO₂ max / 40 % VO₂ max), one week apart, matched for workload. Before and after exercise, subjects underwent neuronavigated TMS (figure of eight coil) followed by testing of pinch, grip strength and dexterity.

Results: Short interval intracortical inhibition (SICI) decreased in the less affected hemisphere following MICE (22.03 % (11.14) to 30.5 % (20.63), $p = 0.04$), while there was no change following HIIT (25.22 % (14.97) to 32.19 % (22.04) ($p=0.186$)). Pinch strength in the affected hand was also significantly lower following MICE.

Conclusion: MICE may be superior to HIIT in acutely influencing neural networks of a non-exercised muscle.

Key words: Aerobic Exercise, TMS, Stroke Recovery

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List of Abbreviations and Symbols

AMT	Active Motor Threshold
ARAT	Action Research Arm Test
AE	Aerobic Exercise
BDNF	Brain-derived neurotrophic factor
BBT	Box and Blocks Test
BF	Breathing Frequency
CSE	Corticospinal Excitability
CIMT	Constraint Induced Motor Training
EMG	Electromyography
EE	Energy Expenditure
FDI	First Dorsal Interosseous
FMT	Fugl-Meyer Test
GABA	Gamma-aminobutyric Acid
GXT	Graded Exercise Test
HR	Heart Rate
HIIT	High Intensity Interval Training
ISI	Interstimulus Interval
ICF	Intracortical Facilitation
LICI	Long Interval Intracortical Inhibition
LTD	Long-Term Depression

LTP	Long-Term Potentiation
MSO	Maximum Stimulator Output
M1	Primary Motor Cortex
MICE	Moderate Intensity Continuous Exercise
MEP	Motor Evoked Potential
ms	Millisecond
mV	Millivolts
NIBS	Noninvasive Brain Stimulation
PP-TMS	Paired Pulse Transcranial Magnetic Stimulation
RPE	Rate of Perceived Exertion
RMT	Resting Motor Threshold
SICI	Short-Interval Intracortical Inhibition
TV	Tidal Volume
TCI	Transcallosal Inhibition
TMS	Transcranial Magnetic Stimulation
VCO ₂	Volume of Carbon Dioxide
VO ₂	Volume of Oxygen
VO ₂ max	Maximal Oxygen Intake
VE	Minute Ventilation

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Chapter 1: Introduction

The incidence of stroke has seen a marked increase in Canada making it an important area for research and intervention. Stroke is now ranked as the third leading cause of death in Canada behind heart disease and cancer.¹ In one year approximately 62,000 Canadians will be hospitalized due to a stroke,² putting a tremendous stress on our healthcare system. Additionally, approximately 300,000 people are currently living with the effects of stroke.³ Those living with the long-term effects of stroke often require health care services long after their initial hospitalization. Because of this, it is important to find ways to help people continue their recovery after initial hospitalization and inpatient rehabilitation.

The effects of stroke are devastating: approximately 66 % of people who experience a stroke will be left with some form of disability.⁴ Due to stroke, the Canadian economy loses 3.6 billion a year in lost wages, long term disability, and patient-related health care cost.⁵ The lasting effects of stroke on patients and their immediate family makes it a chronic disease that has lifelong effects.

Following stroke, motor impairments are the most noticeable deficit. These impairments are very debilitating because they interfere with individuals' ability to perform activities of daily living. People post-stroke must relearn many routine physical tasks, by a process called motor learning, which is a primary focus of neurorehabilitation. This type of learning requires neuroplasticity and in rehabilitation specifically, use-dependent plasticity which is induced by performing repeated task practice.^{6,7} Several

groups have proposed that aerobic exercise (AE) can be used to ‘prime’ the brain and make it more amenable to use-dependent plasticity. Creating an environment that primes the central nervous system for neurorehabilitative therapies, may enhance the effect of these therapies and potentiate the level of motor recovery in individual’s post-stroke.

The purpose of this study was to understand how an acute bout of AE affects the excitability of the brain in chronic stroke patients. The first aim was to determine how the brain excitability of individuals was affected by a single session of two different AE training methods and which neural pathways were modulated by it. These cortical networks were measured using transcranial magnetic stimulation (TMS) which uses varying stimulation paradigms to probe inhibitory and facilitatory networks. A second aim of this study was to understand how motor function was affected following two different AE training methods. The overarching aim was to provide insight into how to use AE effectively during stroke neurorehabilitation. An effective pre-AE session may prepare the brain for the more intensive therapy and prime it to undergo use-dependent plasticity.⁸

This thesis contains three chapters. Chapter One is a literature review that introduces important concepts related to the current understanding of stroke and the role of the primary motor cortex (M1), the area of the brain responsible for planning, control and execution of voluntary movements. The physiology of AE and its use in post-stroke recovery will also be discussed. Motor learning and its role in motor recovery following stroke is also elaborated upon in relation to TMS. Chapter Two contains a manuscript prepared for submission to the journal, Neurorehabilitation and Neural Repair. The study

compared two AE training methods on neural networks among people with chronic stroke. Cortical excitability and intracortical networks were measured using paired pulse TMS techniques. Lastly, Chapter Three provides more in-depth discussion of the results expanding upon how these results answered the primary research questions, and addresses potential study limitations and future research directions.

Research Questions

The three primary research questions addressed in this thesis are:

1. Do different intensities of AE lead to different changes in intracortical inhibitory and facilitatory networks in stroke survivors?
2. What are the effects of different acute AE methods on overall excitability of the cortico-spinal tract responsible for upper limb muscles in stroke survivors?
3. Does alteration in motor cortical networks from varying acute AE intensities lead to immediate changes in manual dexterity and grip strength in stroke survivors?

An Overview of Stroke

The Etiology of Stroke

Stroke is defined as the abrupt onset of symptoms of focal neurological dysfunction, lasting more than 24 hours, caused by acute vascular injury to parts of the brain.^{9,10} There are two types of stroke, ischemic and hemorrhagic. Ischemic stroke occurs in 80 % of cases and is the result of inadequate blood supply to parts of the brain.⁹ Hemorrhagic stroke is less common occurring in 20 % of cases and results from a spontaneous hemorrhage, which is an uncontrolled leaking of blood into surrounding brain tissue or on the surface of the brain.^{9,11}

The probability of experiencing a stroke increases significantly during the sixth decade of life. Individuals with a greater number of associated risk factors such as: vascular disease, hypertension, smoking, poor cardio-respiratory fitness, and diabetes have a higher likelihood of experiencing a stroke.¹²⁻¹⁵ These risk factors are considered modifiable and can be addressed with increased fitness, proper diet and nutrition^{16,17} making primary and secondary stroke prevention an important field of study for clinical research.

Population Impact of Stroke

Stroke is the second leading cause of death in the world and the leading cause of disability-adjusted life year,^{18,19} a measure used to quantify burden in terms of years lost due to illness.²⁰ From the most recent worldwide estimates, 16.9 million people experienced a stroke in 2010, and 5.9 million people died.¹² In Canada, Newfoundland

and Labrador has the highest rates of stroke, making the issue particularly pressing for this population.²¹ Taken together, these statistics demonstrate an urgent need to address primary and secondary stroke prevention through research and intervention.

Types of Stroke

There are four main brain areas that can be affected by stroke (cortical, subcortical, cerebellar and brainstem) and each present with unique clinical symptoms. Cortical strokes are caused by the occlusion or rupture of more distal arteries. Clinically patients with cortical stroke present with: aphasia, neglect, homonymous visual field deficits, and cortical sensory loss depending on the cortical region involved.²² Individuals experiencing subcortical stroke present with more unpredictable outcomes. Although subcortical stroke is often smaller than cortical stroke, subcortical strokes are more likely to affect areas of the brain where the fibers responsible for motor control converge, which causes impairments that affect movement and execution of motor tasks.²³ Furthermore, interruption of blood flow to deep cerebral structures like the basal ganglia, thalamus, and other integral subcortical brain structures cause lacunar infarcts, which lead to motor impairments.²⁴ Cerebellar strokes are uncommon, and represent only 2.3 % of all ischemic stroke cases.²⁵ Patients often present with nausea, vomiting, dizziness, and nystagmus, a condition where the eyes move rapidly and uncontrollably.^{26,27} Brainstem strokes are also relatively uncommon and are caused by disruption of the blood supply in the vertebral and basilar arteries.²⁸ Symptoms include dysarthria, dysphagia; contralateral hemiparesis; and ipsilateral cerebellar deficits.²⁹ In addition to different types of stroke,

individuals also experience a wide range of deficits depending upon the specific areas of the brain affected. These deficits also need to be considered in order to design interventions to prevent stroke and improve recovery post-stroke. The wide range of symptoms seen in stroke make it a heterogeneous condition, creating challenges for researchers who tend to favour trials involving homogeneous groups.

Impact of Stroke on the Individual

Following stroke there are number of deficits that develop such as language impairments, somatosensory impairments, cognitive impairments and motor impairments. Language deficits following stroke can affect an individual's ability to maintain interpersonal relationships and return to work.³⁰ Aphasia is a loss or impairment of verbal communication that causes difficulties understanding spoken or written language, repetition, naming, reading and writing.³¹ These impairments persist in 25 % to 50 % of patients in the chronic stage of stroke.³² Somatosensory impairment is present in 50 % of individuals post-stroke,³³ patients present with impaired tactile sensations, problems identifying objects through sensory feedback, inability to explore new environments and issues that complicate motor control of the upper limb.³⁴ Thirty five percent of stroke patients are believed to suffer from cognitive deficits following stroke. Deficits can range from issues with short and long term memory, inability to maintain attention, personality changes and deficits in reading and comprehension.³⁵ In some cases language, somatosensory and cognitive deficits can make it more difficult for people with stroke to re-learn lost abilities, further compounding challenges of motor recovery.

Motor Impairments in Stroke

Motor Consequence of Stroke

After stroke, motor impairment frequently involves the upper limb; creating difficulty in the use of hands and fingers and impeding the ability to perform routine tasks such as feeding and washing.³⁶ Greater than 69 % of stroke patients experience lifelong motor impairments in their upper extremity and an individual's level of arm and hand motor control dictates their ability to live on their own.³⁷ Stroke's impact on motor function is clear; it affects how individuals execute daily functions and contributes to lost productivity in society.⁵ There are several types of motor impairment seen after stroke. Lost functional muscle control and movement³⁸ is a combination of total loss of motor control (paresis) and exaggerated muscle activation (spasticity).³⁹ Paresis or muscular weakness is a common impairment of the upper extremity following stroke, with 56 % of stroke survivors continuing to experience hemiparesis well into the chronic phase of stroke.⁴⁰ Spasticity is another impairment believed to play a large role in the motor dysfunction seen after stroke.⁴¹ Spasticity is a condition whereby certain muscles demonstrate increased tendon reflex activity and hypertonia. The control of muscle tone originates from the inhibition of the medullary reticular formation, and this control is modulated through motor cortical areas.^{42,43}

Recovery of upper limb impairment is often incomplete. It was shown in the Copenhagen stroke study (n=1197) that best functional recovery in activities of daily living was achieved by 9 weeks in mild stroke patients, while it took 20 weeks for the most severely affected patients.⁴⁴ Once patients reach 6 months post-stroke the level of

spontaneous recovery is beginning to plateau^{7,45} and a large number of stroke survivors are left with lifelong disabilities. Innovative therapies are required to boost recovery after the spontaneous 6-month window of recovery.

The degree of motor impairment is dependent on lesion location and size.⁴⁶ Individuals with lesions in the motor-related cortical regions (primary and secondary motor areas), corona radiata, and internal capsule have decreased probability of upper limb functional recovery.^{23,46} Furthermore, it has been shown that the extent of lesion load in the corticospinal tract has a significant linear correlation with motor outcome.⁴⁶ This highlights the importance of the M1 and corticospinal tract in stroke recovery, since damage to these areas is closely related to motor recovery.

The Primary Motor Cortex

Following stroke the M1 plays an important role in functional recovery.⁴⁷ M1 is located in the precentral gyrus and corresponds to area 4 on Brodman's map of the brain. It is responsible for generating and controlling voluntary movement. It receives feedback from the basal ganglia and cerebellum to ensure that all desired movements are executed smoothly. M1 is organized somatotopically, in which areas of the body are mapped onto specific areas of the pre central gyrus.⁴⁸ When motor impairments are present after stroke, they are caused by damage to select white matter tracts like the corticospinal tract that play an integral role in carrying signals from the M1.⁴⁹ Deficits such as paralysis, spasticity, and limb weakness, develop in the upper and lower limbs following stroke.⁷ Damage to white matter tracts like the corona radiata and posterior

limb of the internal capsule has been associated with poorer upper limb movement recovery following stroke.²³ Furthermore, damage to secondary motor cortices also leads to reduced functional recovery of the upper limb post-stroke compared to those who have these areas spared.²³ It is clear how M1 is instrumental in normal motor function, but it is apparent that associated motor cortex areas are also important and should not be overlooked when considering potential targets of interventions following neurological insult.

Role of the Corticospinal Tract in Motor Control

M1 neurons contributing to the corticospinal tract are located mostly in cortical layer 5. Pyramidal cells in this layer project and synapse directly onto motor neurons in the ventral horn of the spinal cord as well as onto spinal interneurons.²² The corticospinal tract is responsible for controlling voluntary movement of the extremities and trunk muscles. This tract has lateral and anterior projections. Eighty percent of the tract crosses over at the level of the pyramids and makes up the lateral corticospinal tract, while 20 % remains uncrossed forming the anterior corticospinal tract. The lateral corticospinal tract is responsible for controlling contralateral limb movements and damage to this tract after stroke leads to severe limb impairment and reduced motor function. A method used to determine integrity and overall excitability of the corticospinal tract is transcranial magnetic stimulation (TMS). We can also assess M1 intracortical networks using TMS. TMS will be discussed in detail later in this chapter.

Neurorehabilitation and Stroke

Plasticity and its Role in Stroke Recovery

Plasticity is the primary agent involved in learning and is responsible for permanent changes in the brain.⁵⁰ The ability of the brain to undergo change, in response to use-dependent learning can be utilized in brain recovery following stroke. Three physiological changes in the brain are believed to mediate spontaneous recovery: i) upregulation of cell growth and repair proteins (neurotrophins); ii) alteration of existing neuronal pathways; iii) formation of new synaptic connections through neuroplasticity.⁵¹ Evaluating and designing intervention strategies that induce or enhance beneficial neuroplastic processes is a primary goal of neurorehabilitation, and in stroke patients, neuroplasticity plays a fundamental role in motor learning and rehabilitation.⁵² Long term potentiation (LTP) is defined as a long lasting increase in the size of the post synaptic response due to constant afferent stimulation.⁵³ M1 can undergo reorganization by LTP through repeated performance of motor learning tasks.⁵⁴ Motor training has been shown to lead to functional changes in motor associated brain regions.⁵⁵ Relearning movement is encoded by changes in cortical circuitry that is induced by synaptic change.^{55,56} Modification of synapses and growth of new dendritic connections is supported by growth promoting proteins called neurotrophins.⁵⁷ Neurotrophins are proteins that are believed to mediate central synaptic plasticity.⁵⁸ After stroke, these neurotrophins become upregulated in order to support plasticity and recovery.⁵⁹ The evidence connecting exercise and plasticity will be further discussed later in this chapter.

Trajectory of Recovery

The success of rehabilitation and the extent of functional recovery is dependent on the amount of brain tissue spared and the capacity for relearning.^{38,60} Certain stroke patients never regain arm function and less than 20 % will achieve complete recovery.^{38,61} Most spontaneous recovery is believed to occur within the first 3 months following stroke.⁶² Being able to measure cortical reorganization and the changes in existing neural networks, may allow us to evaluate a patient's recovery progress. Recovery in the motor system is highly variable following stroke, the largest improvements in motor impairments have been shown to occur 30 days following stroke,⁶³ while those who are more initially impaired, show substantial improvement 90 days post-stroke.⁶² Recovery from language deficits is thought to follow a similar time course, patients with severe aphasia take 10 weeks to reach final level of language function, while patients with mild aphasia take 2 weeks to achieve maximum language function.⁶⁴ However, language recovery has been shown to extend past the acute phase of stroke.⁶⁵ Current rehabilitation aims to capitalize on the window of spontaneous recovery in the acute phase post-stroke to maximize the relearning of lost function. However, people in the chronic phase of stroke (greater than 6 months post-stroke) outside the window of recovery, still need therapies that promote recovery.

Importance of Rehabilitation in Stroke Recovery

The goals of rehabilitation following stroke are for patients to relearn abilities such as speech, hand dexterity and walking, which are important in everyday

function.^{66,67} Rehabilitation aims to maximize patient's physical and psychological recovery.⁶⁸ There are 4 general steps in rehabilitation: identifying the patients' needs, devising attainable goals for recovery, delivering interventions that aid in achieving the goals, and finally, assessment of progress that individuals have made during rehabilitation.⁶⁹ Motor learning is the key mechanism by which lost physical function and movement is relearned. This form of learning is achieved by providing task specific and context specific training interventions.⁶⁹ The sooner rehabilitation is delivered the more effective it is,⁷⁰ and the greatest gains from rehabilitation are expected in the acute stage of stroke (less than 6 months).⁷¹ As mentioned, this window of plasticity occurs when there is a cascade of changes occurring in the brain creating a critical period for recovery.⁵⁹ It has been shown that delayed delivery of therapy (> 30 days of stroke) leads to poorer functional outcome.⁷² The plastic changes that occur early after stroke begin to diminish with time, thus emphasizing the need for strategies that keep this window open into the chronic phase of stroke.⁵⁹ Motor learning and spontaneous recovery (when patients improve on their own as the brain heals) have an overlapping role in affecting patient's physical improvements during the acute phase of stroke.⁶⁷ It is evident that repetitive practice of a specific task leads to improved recovery⁷³ but less is known about the optimal intensity and length of training to maximize functional recovery. Maintaining plasticity processes beyond the typical window of 6 months has been the focus of several emerging training such as constraint induced motor training (CIMT)⁷⁴, brain stimulation (transcranial direct-current stimulation)⁷⁵ and pharmacological (fluoxetine trials)

therapies.⁷⁶ The principles that should be considered when designing training protocols will be discussed later in this chapter.

Emerging Therapies to Enhance Plasticity

Improving hand function and reducing impairment following stroke calls for novel and innovative approaches to enhance plasticity and ‘break through’ the recovery plateau. New strategies are rooted in the principles of motor learning and the use of repeated practice to maximize recovery. CIMT is one type of training that capitalizes on motor learning by encouraging use of the affected hand by restricting the non-paretic hand. This type of training is promising because it has been shown to lead to motor improvements in people in the chronic phase of stroke.⁷⁷ CIMT has been shown to enlarge the cortical representation in the affected hand⁷⁸ and fMRI imaging has showed that in response to CIMT there is altered neural activity.⁷⁹ Robot training is another intervention targeting motor impairments following stroke. This type of training is primarily useful for upper limb recovery.⁸⁰ It also employs the tenants of motor training using intensive and task oriented practice to promote functional recovery.³⁸ Robotic training also has the added benefit of providing real time feedback allowing synchronization of sensory and motor systems facilitating neural plasticity.⁸¹ Bimanual training uses the non-paretic limb to promote functional recovery in the affected limb through facilitative coupling between upper limbs.⁸² It is believed that through practice of bilateral symmetrical movements, the non-affected hemisphere facilitates activation of the affected hemisphere leading to improved movement of the impaired limb.⁸³ Chronic

stroke patients undertaking bilateral training have been shown to improve function of the upper limb.⁸³

Neuroplasticity can also be augmented in the brain by other mechanisms besides motor training. Noninvasive brain stimulation (NIBS) such as repetitive transcranial magnetic stimulation and transcranial direct-current stimulation are interventions that alter brain excitability in the cortex.⁸⁴ These methods exploit the interhemispheric model to augment neuroplasticity and enhance hand function.⁸⁵ The model stipulates that following stroke decreased motor output from the affected hemisphere coupled with excessive inhibition from the unaffected hemisphere to the affected hemisphere, leads to motor deficits.^{85,86} NIBS can improve motor function in stroke patients by either decreasing the excitability of the non-affected hemisphere or increasing the excitability of the affected hemisphere.⁸⁷ Pairing a motor task with NIBS has shown to induce more plasticity and greater functional improvements in chronic stroke patients.^{88,89} Unfortunately, following stroke there are a whole host of other issues patients face such as poor cardiovascular health, obesity and hypertension. AE is also a ubiquitous but often overlooked aspect of health promotion in cerebral vascular disease. AE, when implemented with the correct dosage can improve fitness and metabolic profiles and emerging research suggests that AE can also improve brain health. Unfortunately, AE is not routinely applied in stroke rehabilitation.⁹⁰ Thus, clinicians and researchers are developing best practice guidelines and knowledge translation tools in order to enhance AE implementation.

Benefits and Overview of Aerobic Exercise

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure.^{91,92} The term exercise, is often used interchangeably with physical activity, when actually it is a subcategory of physical activity.^{91,93,94} Exercise is a planned, structured, repetitive and purposeful activity aimed to improve or maintain an individual's physical fitness.⁹¹ There are numerous effects of exercise such as neuromuscular adaptations, muscle atrophy, and cardiovascular changes.⁹⁵ Exercise can be further separated into two main categories; aerobic training and resistance training. These types of training challenge different systems. While AE causes increases in volume of oxygen (VO_2) which is a person's ability to consume and utilize oxygen, resistance training (also called strength training) promotes muscle strengthening and hypertrophy.⁹⁶⁻⁹⁸

The benefits of AE on cardiovascular health are well documented. Men and women who engage in higher levels of AE have a significantly lower relative risk of death.⁹⁹ Furthermore, it has also been shown that encouraging individuals who are deconditioned and sedentary to engage in exercise has a large effect on health status.⁹⁹ With our current understanding of the benefits of AE, encouraging patients in the chronic phase of stroke to undertake AE may have beneficial effects on their health and neurological status.^{100,101} There are still several gaps in our understanding of how to best use AE to enhance stroke recovery, a key element of which, is the creation of evidence

supporting the appropriate intensity of exercise to maximize stroke recovery in the chronic phase of stroke.^{102,103}

The Effects of Aerobic Exercise in the Healthy Brain

In the general population, AE promotes plasticity and has neuroprotective effects on the central nervous system.¹⁰⁴ Findings from animal studies have shown that engaging in exercise for prolonged periods leads to increases in hippocampus neuron formation.¹⁰⁵ A seminal study by Eriksson *et al.*, 1998, showed that in the human hippocampus, new neurons could form¹⁰⁶ and individuals performing AE over an extended period of time have larger hippocampal size.¹⁰⁷ Animal studies have also shown that AE leads to the activation of growth proteins which are vital for neural stem cell growth and survival.^{108,109} In addition, chronic AE leads to increases in grey and white matter of the prefrontal cortex in older adults.¹¹⁰ Smith *et al.*, 2014 suggested that partaking in high levels of physical activity maintained over an extended period of time can increase the capacity for cortical plasticity.¹¹¹

Acutely, AE has been shown to increase cerebral blood volume¹¹² and upregulate the neurotrophin brain-derived neurotrophic (BDNF) and its TrkB receptor.^{107,113} Increases in BDNF are believed to be one of the mechanisms by which AE exerts positive benefits on learning and memory.¹⁰⁷ Acute bouts of AE have been shown to modulate intracortical networks of the brain, leading to decreased inhibition and increased facilitation^{111,114} Also, performing an acute bout of AE before learning a motor task has been shown to lead to improved long term retention of the practiced motor

task.¹¹⁵ Furthermore, acute exercise has the potential to act globally within the brain, not just in the specific circuits controlling the exercising muscles, due to its ability to trigger critical molecular and cellular processes that support brain plasticity.^{104,114} However, it is less known about how AE affects the brain affected by stroke and particularly the intracortical networks within the M1.

Effects of Aerobic Exercise in the Brain Affected by Stroke

Although there is accumulating evidence supporting the benefits of AE in the healthy brain, there is less certainty about how AE influences the brains of people affected by stroke. For example, following stroke, the brain undergoes a cascade of changes which may influence how the brain responds to AE.¹¹⁶ However, from a cardiovascular standpoint, the benefits of AE are well documented in stroke populations.^{100,101,117,118} In animal stroke models it has been shown that following AE there is an increase in neurotrophin release, enhanced synaptogenesis and dendritic branching.^{119,120} AE has also been shown to improve spatial memory in stroke models¹²¹ as well as increase working memory and learning.¹¹⁹ Executive function, a component of cognition, is important for the execution of complex tasks.¹²² Amongst patients with stroke prolonged AE led to improvement in overall cognition, measured using the Montreal cognitive assessment.¹²³ Clearly more research is required to decipher how cortical excitability is influenced by exercise the brains affected by stroke and whether this translates to any improvement in functional outcomes.

Different Types of Aerobic Exercise (HIIT versus MICE)

During AE, oxygen is metabolized to produce energy.¹²⁴ We utilized two AE training methods: moderate intensity continuous exercise (MICE) and high intensity interval training (HIIT), both of which induce physiological adaptations.¹²⁵ These training modalities differ in the intensity of the exercise session. MICE training requires continuous moderate to vigorous intensity continuous exercise over a set length of time (usually 20-30 min) without intervals of rest.¹²⁶ MICE is recommended for patients post-stroke,^{127,128} and guidelines indicate that stroke patients should work at 40 %-70 % of peak VO₂ or heart rate reserve for 20- 60 minutes, 3-7 days per week.¹²⁷ Measured in a different way, MICE is performed at 3 to 6 Metabolic Equivalents of Task, equivalent to a brisk walk at 4.8 to 6.4 kph in healthy adults.⁹³ MICE has been used routinely in cardiac rehabilitation programs and aims to improve stroke patients' aerobic capacity, gait endurance and vascular risk factors.^{101,127} Less is known about the impact of MICE on cortical excitability and even less so after stroke.

HIIT is characterized by brief, repeated bursts of relatively high intensity exercise separated by periods of rest or low intensity exercise. The high intensity bursts are alternated with recovery periods, which are designed to mitigate fatigue and increase cardiovascular safety.¹²⁷ Generally, this protocol involves less than 10 minutes of intense training within an exercise session that is less than 30 minutes long.¹²⁹ There are many types of HIIT protocols, which all aim to maximize the amount of time spent at high aerobic intensities. Short interval HIIT and long interval HIIT are designed to spend the greatest amount of time at peak VO₂. They differ in the length of time spent at high

intensities and active rest periods.^{127,130} Low-volume HIIT aims to achieve the greatest neuromuscular intensity.¹³¹ These types of exercises have received a lot of attention because they are considered to be more effective in improving aerobic capacity and other health outcomes in healthy adults and people with cardiovascular disease.^{127,132} Furthermore, in cardiac patients HIIT training has been shown to lead to greater cardiorespiratory improvements represented by an increase in peak VO_2 .¹³³ However, the superiority of HIIT over more conventional training such as MICE is not certain. In a recent randomized control trial among patients with heart failure, both HIIT and MICE led to improvements in fitness and metabolic markers.¹³⁴ In stroke populations, little is known about how different AE intensities affects cortical excitability in the brain pointing to a clear gap in literature.

Exercise Intensity and Prescription

When designing physical activity plans there are four key components to consider: frequency of exercise, intensity of exercise, length of exercise (referred to as time), and type of exercise. Together these components are known as the FITT principle,^{135,136} and they are important parameters when considering the appropriate dose of exercise. Dosage is important concept in rehabilitation when implementing interventions that foster relearning of complex motor tasks through task-specific training,¹³⁷ however “how much more?” and “for whom?” remain unanswered questions.¹³⁸ These unanswered questions also exist when considering aerobic exercise prescription for stroke. As highlighted above, an important principle is intensity, but there

are many interpretations of the term ‘intensity’ in rehabilitation. Two popular definitions of intensity in terms of task training are: *number of task repetitions* and *amount of time* dedicated to a task. However, additional questions concerning AE intensity should also include *how much work is being performed* or *the magnitude of the effort required* while performing an activity or exercise.¹³⁵ To measure intensity in this way, oxygen consumption and the percentage of heart rate reserve are calculated.¹³⁶ Furthermore, part of understanding the appropriate dose of exercise for stroke recovery is understanding the dose required to elicit a change in cortical excitability of motor pathways involved in executing motor output.

Currently there is a lack of evidence identifying the appropriate dose of exercise required to induce a beneficial response in the cortical networks of chronic stroke patients. This includes a paucity of information about intensity. As mentioned previously there is convincing evidence of the benefits of long term exercise on cognitive function, neurogenesis, muscle strength and cardiorespiratory fitness in healthy older adults.^{139,99} In terms of effects of on brain activity, it has been shown that an acute bout of exercise in healthy individuals causes changes in inhibitory cortical networks, which is implicated in neuroplasticity.¹⁴⁰ Whether HIIT or MICE affects brain excitability in people with stroke and the extent to which the potential changes in excitability would affect hand function is unknown.

Measuring Plasticity and Recovery in the Upper Limb After Stroke

When discussing measurements of upper limb recovery after stroke it is helpful to consider measurement frameworks such as the international classification of function framework.¹⁴¹ In this framework, upper limb recovery is measured at the “functional level” by testing or asking the patient how they use the limb in everyday tasks. To probe deeper, tools that examine hand or finger strength and dexterity indicate level of impairment. Finally, techniques such as functional magnetic resonance imaging and TMS can measure upper limb recovery at the mechanistic or neurobiological level. Combining these tests enable researchers and clinicians to relate changes that occur in the brain to meaningful changes in arm and hand ability.

Functional Outcome Measures Assessing Upper Limb Recovery

Functional outcome measures assess different components of upper limb function including range of motion, strength, coordination and ability to appropriately activate muscles. The most pronounced deficit post-stroke is hemiparesis,¹⁴² the inability to activate motor units.¹⁴³ The most commonly used tests of upper limb ability are: Fugl-Meyer Test (FMT), Action Research Arm Test (ARAT) and Box and Blocks Test (BBT). The FMT assess the level of arm and joint mobility.¹⁴⁴ Patients are asked to complete progressively complex movement combinations and the results are scored by a trained observer. During the ARAT, the individual is asked to move and manipulate small and large objects. Each task is timed and the score reflects gross and fine motor activity limitation of the upper limb.^{144,145} The BBT gross manual dexterity,¹⁴⁴ assesses how well an

individual is able to grasp, transport and release small blocks from one compartment to another.¹⁴⁶ The score reflects the number of blocks moved. Hand grip and pinch strength are also valuable measures of upper extremity function in chronic stroke subjects.^{147,148} Typically, patients squeeze a hand dynamometer and the forces are recorded. Measures of strength and manual dexterity are easy and quick to obtain, compared to the FMT and ARAT which have multiple components and take a longer time to administer.

Measuring Mechanisms of Recovery

To understand how plasticity and recovery takes place in the brain following injury, neuroimaging and neurophysiological tools such as TMS, positron emission tomography (PET), blood oxygen-level dependent functional magnetic resonance imaging (BOLD-fMRI), are some ways to measure brain activity and recovery. BOLD-fMRI and PET are used to identify function-related areas by observing the brain hemodynamic response during a specific task. Those areas in the brain that become active during a task represent active neurons.^{149,150} BOLD-fMRI and PET are beneficial because they produce images with high temporal and spatial resolution.⁶⁶ These techniques are limited because they require expensive equipment and specialized operators. Furthermore, these techniques only measure blood flow and activity of neurons, but are not able to assess the inhibitory and facilitatory networks at work in the brain. TMS is used to probe cortical excitability and cortical reorganization in stroke patients,⁶⁶ and is ideal to measure M1 excitability and probe intracortical networks. There is no

requirement for individuals to perform a movement to obtain a TMS measure as is the case for BOLD-fMRI and PET.

TMS to Measure Integrity of the Corticospinal Tract

TMS is a non-invasive method that uses magnetic pulses to elicit an electrical current in the cortical neuronal networks beneath the scalp.¹⁵¹ In order to quantify the transmission of the signal from stimulated brain regions we use electromyography (EMG) of the target muscle. Muscle activity is represented by Motor Evoked Potentials (MEPs). MEPs are electrical potentials that are collected from a muscle of interest after direct stimulation of M1 with TMS (Figure 1). The most common way MEPs are quantified is by measuring the ‘peak-to-peak’ amplitude. This amplitude reflects the integrity of the corticospinal tract and the excitability of M1.¹⁵²

TMS works by using a coil which produces a magnetic pulse when a current is passed through it. Pulses can vary in size; the largest that can be delivered has a magnetic field of 2 tesla (units of magnetic field).¹⁵³ Using the TMS coil the delivery of the stimulation can be focused on a brain region of interest and elicit activation of motor neurons. The type of cortical neurons activated depend on coil angle placement on the head and the intensity of the magnetic pulse. The optimal coil position on the head is 45° degrees (Figure 2) which induces an anterior to posterior current.¹⁵⁴ TMS is useful for two main purposes: 1) to measure the integrity (or excitability) of the corticospinal tract

(single pulse methods) and 2) to probe the function of inhibitory and facilitatory cortical networks (paired pulse methods). These methods are outlined in Table 1.

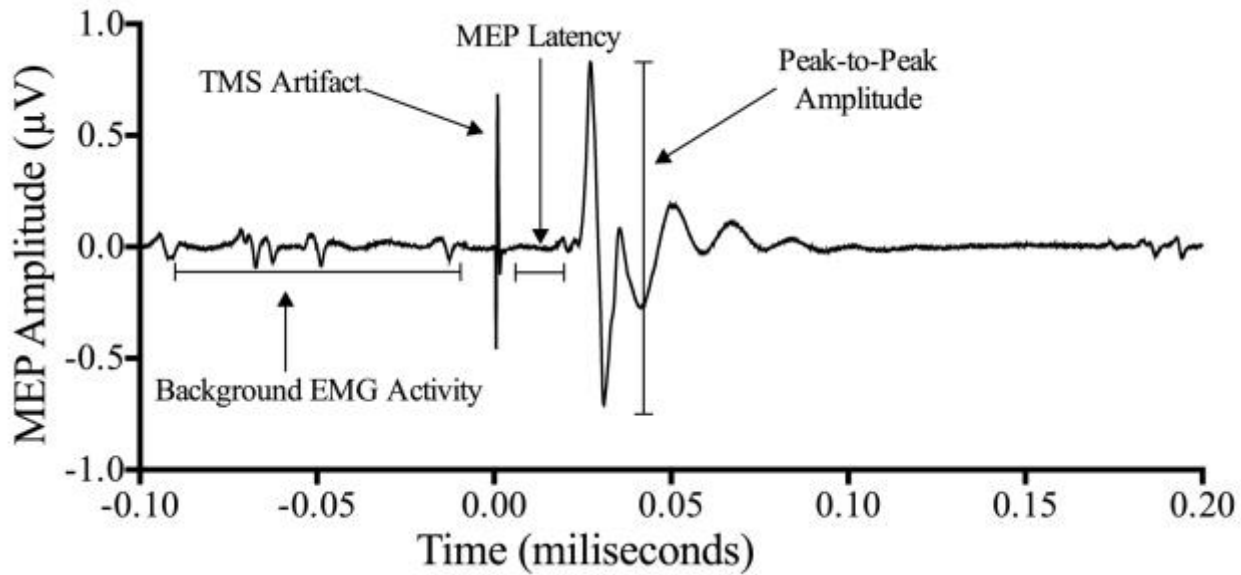


Figure 1. Motor evoked potential (MEP) from first dorsal interosseous (FDI) muscle following stimulation of the primary motor cortex (M1). Background EMG activity is resting level activity in the muscle before TMS stimulation is delivered. MEP latency represents the time it takes for the stimulation to elicit a response in the muscle of interest. Peak-to-Peak amplitude represents the activation of motor neurons following direct stimulation of M1.



Figure 2. Participant seated in TMS chair and coil placed at 45° degrees to the scalp

Table 1. List of TMS measures

TMS paradigm	What it measures	How its measured
Single pulse		
Resting Motor Threshold (RMT)	Assess overall corticospinal excitability	Maximal stimulator output (MSO) required to achieve 5 out of 10 MEPs $\geq 50 \mu V$ ¹⁵⁵
Active Motor Threshold (AMT)	Assess overall corticospinal excitability, during contraction	Maximal stimulator output (MSO) required to achieve 5 out of 10 MEPs $\geq 200 \mu V$ ¹⁵⁵
Transcallosal Inhibition (TCI)	Assess transcallosal connection between primary motor cortices	Maintain a contraction 150 % of maximum voluntary muscle contraction (MVC) and stimulator intensity set at test stimulus (1mV) ¹⁵²
Paired Pulse		
Short intracortical Inhibition (SICI)	Measures GABA _A receptor activation in pyramidal M1 neurons	Subthreshold stimulus: (80 % of RMT) preceding a Suprathreshold stimulus (1 mv peak-to-peak) (ISI) :2-5ms - measure degree of suppression of test stimulus ^{156,157}

Intracortical Facilitation (ICF)

Measures glutamatergic neurotransmitter activity in pyramidal M1 neurons

Subthreshold stimulus: (80 % of RMT) preceding a Suprathreshold stimulus (1 mv peak-to-peak) (ISI) :9-21ms – measures degrees of facilitation of MEP¹⁵⁷

Measures of Corticospinal Tract Integrity

Single pulse TMS involves delivering a single pulse to the cortical area of interest. Using single pulse measure we can obtain the motor threshold, which is believed to reflect membrane excitability of corticospinal neurons in M1 and the spinal cord.¹⁵²

There are two types of motor threshold: resting motor threshold (RMT) and active motor threshold (AMT). RMT is the minimum amount of maximum stimulator output (MSO) or intensity required to elicit a 50 μ V MEP in the muscle of interest. To ensure reliability, the intensity being stimulated must produce at least 5 out of 10 MEPs that are equal to or greater than 50 μ V. AMT is similar to RMT except that it involves an individual contracting the muscle of interest at 10 % of their maximum voluntary contraction and then determining the MSO that elicits a MEP of 200 μ V or greater, 5 out of 10 MEPs.

Measures of Transcallosal Connections

Transcallosal inhibition (TCI) is a form of inhibition that regulates interhemispheric communication. It has been shown that the unaffected hemisphere inhibits the affected hemisphere through abnormal interhemispheric inhibition and restricts motor function after stroke.¹⁵⁸ This network is probed by delivering a single subthreshold pulse to M1 while a person maintains a steady contraction of the contralateral muscle.¹⁵² The TCI paradigm involves an individual contracting at 50 % of

their maximum voluntary muscle contraction (MVC) and being stimulated at 150 % of their RMT. This TMS paradigm is believed to look at the transcallosal communication between motor cortices. TCI could be an important outcome in stroke recovery trials since in chronic stroke patients that have poor motor recovery it appears that there is a greater level of interhemispheric inhibition from the intact M1 hemisphere to the lesioned M1 hemisphere.⁸⁶ The increased inhibition of the lesioned M1 leads to decreased excitability and poorer functional recovery in patients with stroke,¹⁵⁹⁻¹⁶¹ while stroke patients with higher level of ipsilesional M1 excitability have better clinical outcomes.^{159,162}

Measures of Intracortical Networks in the Primary Motor Cortex

Paired pulse TMS (PP-TMS) is a TMS paradigm used to measure inhibitory and facilitatory interactions in the brain.¹⁵² PP-TMS involves delivering a subthreshold conditioning stimulus and a suprathreshold test stimulus at different inter stimulus intervals (ISI).¹⁵² The subthreshold stimulus is delivered at 80 % of RMT and the test stimulus is at an intensity that elicits a 1 mV MEP. The initial stimulus is not strong enough to induce the firing of pyramidal neurons but activates them into a primed state, making them more susceptible to firing when a second suprathreshold stimulus is delivered.¹⁶³

Short interval cortical inhibition (SICI) is an inhibitory network mediated by GABA_A receptors and activated using a PP-TMS ISI between 1-5ms.¹⁵⁶ Another form of inhibition is long-interval cortical inhibition (LICI) an inhibitory network similar to SICI

but is mediated by GABA_B receptors and has an ISI of 50-200ms.¹⁵³ Inhibitory synaptic transmission is mediated by GABA neurotransmitters and is present in all layers of the cortex.¹⁶⁴ Facilitatory networks also exist in the cortex and can be measured using TMS, probing intracortical facilitation (ICF). This network is regulated by glutamatergic receptors and can be activated using a PP-TMS ISI between 10-25ms. In this paradigm the initial conditioning stimulus is strong enough to activate cortical neurons but not strong enough to initiate a descending volley of neuron activation and MEP production.¹⁵³ The second stimulus that follows is above threshold and induces a MEP.¹⁵³ A summary of TMS measures is provided in Table 1.

Within the M1 there are inhibitory and facilitatory networks that play a critical role in regulating the output of M1 pyramidal neurons.¹⁶⁵ Singh *et al.*, 2014 showed that following AE there is a decrease in intracortical inhibition, which is implicated in LTP-like plasticity.^{111,140} Furthermore SICI reduction has been shown to correlate with enhanced practice dependent plasticity in healthy individuals.^{111,166} Therefore if exercise causes a release of inhibition it should create an environment that is more conducive to neuroplasticity.^{140,167} Blicher *et al.*, 2009 demonstrated that in chronic stroke patients performing a repetitive thumb movement task, there was an increase in ICF and a decrease in SICI.¹⁶⁸ This finding suggests that these intracortical networks are amenable to change even in the chronic phase of stroke. Less is known about how AE affects these intracortical networks in chronic stroke. Addressing this gap is a main aim of this thesis. The study described in this thesis seeks to understand how intracortical networks and

transcallosal connections are influenced by two AE methods (HIIT and MICE) in patients with chronic stroke.

Summary

Advances in access to medical care combined with increased life expectancy in an ageing population results in more people having strokes, surviving the initial event and living longer with the sequelae of stroke. Rehabilitation is taking on an even greater importance to maximize positive motor recovery and reduce dependence for care. There are questions that remain with respect to dose and intensity of rehabilitation interventions required to foster continued plasticity in the chronic phase of stroke, especially with regards to cortical excitability of motor pathways involved in executing motor output.

The present research was conducted with the aim of comparing the acute effects of two methods of AE on cortical excitability and intracortical networks in chronic stroke survivors. If AE positively affects cortical circuitry that is believed to play a role in upper limb motor function impairment,⁸⁶ then it may potentiate the effect of therapies (such as skilled reach training) employed to treat chronic stroke patients.

Co-authorship Statement

All individuals listed on the manuscript have satisfied the criteria for authorship. A version of this manuscript is being prepared for submission to Neurorehabilitation and Neural Repair. The roles of the authors were as follows: Beraki Abraha had primary responsibility for this thesis: designed the study, collected and analyzed the data, prepared the manuscript and had final approval of the version to be published. Since we work with a clinical population, there are multiple authors involved. Those included were: Katie P. Wadden: who assisted in data collection, and provided review of the manuscript, Elizabeth M. Wallack: assisted in manuscript preparation and revision, Liam P. Kelly: helped design the exercise training parameters, Michael T. King: assisted in manuscript preparation and revision, Michelle Ploughman: as primary supervisor provided input on the design of the study, revision and preparation of manuscript.

Chapter 2: Manuscript

The Effects of High Intensity Interval Training versus Moderate Intensity Continuous Exercise on Neural Networks in Chronic Stroke.

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Background: Aerobic exercise (AE) upregulates neurotrophins and alters brain excitability post-stroke and could potentially be paired with impairment-specific tasks to enhance relearning. Using transcranial magnetic stimulation (TMS) we compared the acute effects of moderate intensity continuous exercise (MICE) versus high intensity interval training (HIIT) on cortical excitability.

Methods: Patients (n=13) >6 months post-stroke underwent graded maximal exercise test (GXT) to determine exercise workload. In this crossover trial, they completed 25 min MICE (60 % VO₂ max) and HIIT (80 % VO₂ max / 40 % VO₂ max), one week apart, matched for workload. Before and after exercise, subjects underwent neuronavigated TMS (figure of eight coil) over the motor area corresponding to the first dorsal interosseous muscle (FDI) of each hand followed by testing of pinch, grip strength and dexterity (box and blocks test). Resting motor threshold (RMT), intracortical facilitation (ICF) and short interval intracortical inhibition (SICI) were quantified using motor evoked potentials (MEP).

Results: SICI decreased in the less affected hemisphere following MICE (22.03 % (11.14) to 30.5 % (20.63), $p = 0.04$), while there was no change following HIIT (25.22 % (14.97) to 32.19 % (22.04) ($p=0.186$). Increased inhibition in the affected hemisphere was correlated with improvements in pinch strength of the more impaired hand ($R = -0.67$, $p < 0.05$). There were no effects after HIIT and no change in ICF with either training method.

Conclusion: MICE reduced the inhibitory effect of the less affected hemisphere without a change in corticospinal excitability. Our findings point to the usefulness of MICE, but not HIIT in acutely influencing neural networks of a non-exercised muscle. Future research should focus on longer term effects of exercise when paired with targeted upper limb tasks.

Introduction

Aerobic exercise (AE) is a potent intervention that improves brain health by enhancing neuroplasticity and cognition.⁹⁵ AE increases repair-promoting proteins called neurotrophins and may help foster recovery from brain injury such as stroke.^{8,95,169} There are two methods to deliver AE; one in which training is continuous at a moderate to vigorous intensity and the other in which training alternates between high and low intensity, called high intensity interval training (HIIT). HIIT appears to be superior to moderate intensity continuous exercise (MICE) in terms of improved fitness and metabolic health.^{170,171} However, less is known about the optimal AE intensity

(continuous vs. interval) to influence the brain, specifically among people who have experienced stroke.

Transcranial magnetic stimulation (TMS) is a non-invasive technique that can be used to probe neuronal networks to understand how AE affects the intracortical networks within the brain. TMS can assess integrity of the corticospinal tract and corpus callosum, and has the potential to be used as a marker for functional recovery in stroke, based on the presence and quality of motor evoked potentials (MEP).¹⁷² Using TMS, corticospinal excitability can be quantified through resting motor threshold (RMT) and intracortical networks through short interval intracortical inhibition (SICI), and intracortical facilitation (ICF).

Chronic stroke is associated with an imbalance of interhemispheric inhibition and M1 excitability which is believed to affect the movement of the paretic hand.¹⁷³ During movement of the hemiparetic hand, patients with more severe impairment demonstrate greater inhibition of the more affected hemisphere, partially due to suppression from the less affected hemisphere.^{75,86} Not surprisingly, improved functional outcome of the hand and fingers is associated with the return to normal activation in the unaffected and affected hemispheres, respectively.^{160,174} In healthy individuals, an acute bout of MICE¹¹⁴ has been shown to increase cortical excitability in M1 controlling the non-exercised limb. However, it is unknown whether an acute bout of HIIT or MICE can influence cortical excitability and improve paretic hand movement in chronic stroke patients.

Physical rehabilitation following stroke is an arduous process, that does not usually lead to full functional recovery. Many stroke survivors are left with impairments

limiting the use of their paretic hand, thereby impacting their ability to perform activities of daily living.^{175,176} Aerobic exercise has been shown to improve upper limb movement. For example, following a single bout of moderate-intensity body weight supported, treadmill training, chronic stroke patients displayed improved motor function in the hemiplegic hand.¹⁷⁷ However, the link between post exercise changes in cortical excitability and alteration in hand function has not been made.

In this randomized repeated measure study, we aimed to compare the effects of a single bout of AE (HIIT or MICE) on intracortical (inhibitory and excitatory) networks and overall excitability in both hemispheres of stroke patients. Since it has been shown that HIIT training is more beneficial from a cardiorespiratory perspective¹²⁷, we hypothesized that HIIT would have a greater effect on neural circuitry than MICE. We hypothesized that performing HIIT would lead to greater decreases in the level of inhibition and a greater increase in facilitation of the less affected hemisphere when compared to MICE. We collected functional outcome measures (Box and Blocks Test (BBT), pinch strength and grip strength) to determine if a single bout of MICE or HIIT would influence hand strength and manual dexterity.

Methods

Ethics Statement

This study was approved by the local research ethics board and was carried out in accordance with the Declaration of Helsinki on the use of human subjects in experiments. Subjects provided written informed consent before study participation.

Participants

Participants with hemiparetic stroke were recruited from a database of discharged rehabilitation patients. Potential study participants met the following criteria: (1) ischemic or hemorrhagic stroke (> 6 months) confirmed by radiological imaging and clinical assessment (2) deemed safe to participate in exercise by a physician, (3) able to follow two step commands (4) ambulate with/without aid > 10 m (5) reside within 75 km of the study centre and (6) passed TMS screening using a standardized TMS screening form.¹⁷⁸

Study Design

Participants completed a graded exercise test (GXT) to determine maximum heart rate (HR max) and cardiorespiratory fitness (VO₂ max). Values from the GXT were used to calculate intensity of MICE and HIIT. Participants then completed two different AE training sessions in random order, delivered one week apart at identical times of the day. TMS measures were collected from both hemispheres (less affected and more affected) before and immediately following exercise. Measures of hand function (BBT, pinch strength, grip strength) were collected directly after TMS.

Graded Maximal Exercise Test (GXT)

Participants performed the GXT test on a NuSTEP total body recombinant stepper (NuStep, Ann Arbor, MI) using best practice guidelines.¹⁰³ Before undertaking the GXT, participants were asked to refrain from consuming stimulants or engaging in exercise 24 hours before testing. A metabolic cart system (Moxus AEI Technologies, Pittsburgh, PA)

recorded respiratory gas exchange using breath by breath sampling and heart rate (HR) monitored using a chest strap (Polar Electro Oy, Kempele, Finland). Testing began at a load level of 3 (Range 1 to 10) increasing one increment every 2 minutes until exhaustion (each increment equates to approximately a 20-watt increase in workload).¹⁷⁹ During exercise, participants were asked to maintain 80 steps per minute. Exercise testing was halted when participant exhibited two or more signs of achieving peak VO₂; respiratory exchange ratio greater than 1, VO₂ max plateau, HR at the age predicted HR max or rate of perceived exertion (RPE) at least 9/10.

Exercise Interventions

Participants performed both exercise protocols on a NuSTEP total body recombinant stepper. They used only their legs during the exercise session, to minimize activity in the hand muscle being measured, their arms remained unengaged on their lap or at their side. Each exercise session was matched for energy expenditure (EE) to ensure participants were working at similar workloads. A portable metabolic system (Viaysis, Yorba Linda, CA) recorded respiratory gas exchange using breath by breath sampling.¹⁸⁰ HR was monitored throughout the exercise session and RPE was collected every two minutes using the modified 10 point Borg scale. In addition, the age corrected HR reserve was calculated $((\text{maximum heart rate} - \text{resting heart rate}) \times (\text{desired intensity}) + \text{resting heart rate})$ to verify that the workload was in the target range.

HIIT Protocol

The HIIT protocol was adapted from Pohl *et al.*, 2002.¹⁸¹ Participants began with a 5-minute warm up at a speed that was incrementally increased until the workload corresponding to 80 % VO₂ max was reached. The total session was 25 minutes. Participants alternated between 80 % VO₂ max for 2 minutes and active rest at 40 % VO₂ max for 2 minutes. Each load increase was approximately a 20-watt increase in workload. The last active rest period served as a cool down.

MICE Protocol

For the MICE session, participants also worked for a total of 25 minutes. The appropriate intensity required for participants to achieve a workload of 60 % of VO₂ max was determined from the previously conducted GXT. Participants were provided 2 minutes and 30 seconds to warm up and 2 minutes and 30 seconds cool down with MICE lasting 20 minutes at 60 % of their VO₂ max.

TMS Protocol

Foam surface electrodes (Kendall 200 Coviden, Mansfield, MA) were used to measure electromyography (EMG) activity from the first dorsal interosseous muscle (FDI) of each hand, using a bipolar configuration (Ag-AgCl, 2-cm inter-electrode distance). A ground electrode was placed on the lateral epicondyle. All EMG signals were sampled at 40,000 Hz using a CED 1401 power interface (Cambridge Electronic Design 1401, Cambridge, UK) and amplified with a gain of 1000x and filtered with a 3-pole Butterworth filter with cut-off frequencies of 10-1000 Hz (Cambridge Electronic

Design 1902, Cambridge, UK). Data was recorded with a 300ms sweep from 100ms before to 200ms after TMS delivery. Offline analysis was performed using Signal 6.0 software (Cambridge Electronic Design, Cambridge, UK).

Participants were seated upright in an adjustable chair. Magnetic pulses were created using the Magstim Bi-stim 200 stimulator (Magstim Co. Whitland, UK), using D70² figure of eight coil. To ensure proper placement of the TMS coil over M1,Brainsight Neuronavigation software (Rogue Research Inc, Montreal, QC, Canada) was used. This stereotactic system uses a compilation of 150 brain images to render a 3-D brain, to allow specific positioning of the coil over the region of interest in M1. For each participant the optimal coil position was maintained at 45° degrees pointing in an anterior to posterior direction.¹⁵¹ RMT was determined by the minimum intensity required to elicit a MEP, in the FDI muscle, with an amplitude of 50 μ V peak-to-peak in at least 5 of 10 trials.¹⁸² RMT was expressed as a percentage of maximum stimulator output (% MSO).

SICI and ICF were measured using paired pulse stimulation. The subthreshold conditioning stimulus was set at 80 % of RMT and the suprathreshold test stimulus was at an intensity that produced a MEP with a 1 mV peak-to-peak amplitude. Three different interstimulus intervals (ISI) were used: 2 ms, 2.5 ms, 3 ms, to identify which ISI activates SICI inhibitory networks the greatest in chronic stroke patients. To activate the facilitatory networks (ICF) we used an ISI of 12 ms.¹¹⁴ There was a total of 50 stimulations (10 trials for each ISI and 10 trials for the test stimulus) delivered in randomized order. The magnitude of SICI and ICF was represented as a % of

unconditioned MEP (see appendix). A greater % of unconditioned MEP indicates less inhibition.

Functional Measures

Manual dexterity, the ability to make coordinated hand movements¹⁸³, was assessed in each hand using the BBT. This standardized test required participants to transport as many wooden blocks (2.5x2.5x2.5) as possible from one compartment of a box to the other compartment within one minute.¹⁴⁴ The box was oriented lengthwise and placed at the participant's midline, with the compartment holding the blocks oriented towards the hand being tested.

Upper extremity strength was measured using a grip dynamometer (Lafayette Instruments, Lafayette, IN). To ensure maximal force was generated during the grip strength test, participants were seated, shoulders adducted and neutrally rotated, elbow flexed a 90° degree angle, forearm in neutral and wrist between 0° and 30° degrees of dorsiflexion.¹⁸⁴ Pinch strength measured the pressure produced by the distal fingers. Participants were seated comfortably and were required to use their thumb and index finger to apply pressure to the pinch gauge (B&L engineering, Santa Ana, CA).

Data Analysis

To determine whether TMS measures (RMT, SICI, ICF) changed across time, three separate single factor repeated measure analysis of variance (RM-ANOVA) were

conducted with time (Pre, Post) as the within subject factors and exercise intensity (MICE, HITT) as the between subject factor. Significance was set at an alpha level of $p < 0.05$ and effect size was represented as η_p^2 . For significant interactions between time X exercise intensity in the RM-ANOVA, post-hoc analyses were performed. A paired t-test or non-parametric paired t-test was run, depending on normality of the variable. Baseline differences in TMS measures between hemispheres was determined with a paired t-test. Data was tested for normality with the Shapiro-Wilk test with a significance level set at $p < 0.05$. To control for family-wise error, Bonferroni corrections were used for multiple comparisons.

Exploratory Pearson's correlations were used to investigate relationships between functional outcome measures and changes in cortical network excitability. We examined the association between the change score in the functional measures (BBT, grip strength, pinch strength) from the affected hand with change scores of the TMS (SICI, ICF, RMT) measures in the more affected and less affected hemisphere. Change scores were calculated by subtracting the post-exercise measure from the pre-exercise measure. The threshold for significant correlations was $p < 0.05$. All statistical analysis was performed using SPSS 23.0 (IBM Corporation, Armonk, New York).

Results

Participants Characteristics

A total of 13 participants, 63.1 years of age (± 8.71 SD) completed the experimental intervention. One participant was diagnosed with Parkinson's disease after completion of the study, and was therefore excluded from data analyses. As seen in Table

2, participants had low to moderate stroke-related impairment (NIHSS 3.4 (\pm 2.90 SD)) with a wide range of arm impairment from 0 kg grip strength to 37 kg and almost all (9 of 12) had spasticity (MAS 1.33 (\pm 1.49 SD))

Intensity of the Interventions

As seen in Table 3, there were no significant differences in average VO_2 , HR, and EE between HIIT and MICE. However, HIIT resulted in significantly greater carbon dioxide production, and higher peak HR and minute ventilation (Table 3). Average VO_2 in HIIT was higher although not significantly so.

Table 2. Participant Characteristics

Patient	Age/Sex	Type of stroke	Time Since Stroke (months)	Stroke location / Hemisphere	NIHSS	Baseline affected hand grip strength (kg)	Spasticity (MAS)
1	56/M	Ischemic	35	Temporal and parietal lobe/Left	7	32.5	0
2	72/M	Ischemic	19	Posterior internal capsule/Left	1	33.25	0
3	67/F	Ischemic	19	Thalamus/Right	1	19.25	1
4	63/F	Ischemic	63	Parietal lobe/Left	1	0	3
5	46/M	Ischemic	44	Frontal and temporal lobe /Right	3	0	3
6	63/M	Ischemic	42	Medulla/Right	10	37	0
7	76/M	Hemorrhagic	76	Basal ganglia/Right	7	23.5	1 +
8	54/M	Ischemic	47	Frontal lobe/Right	2	22.75	1 +
9	69/M	Ischemic	26	Corona radiata/Left	1	21.75	1 +
10	64/M	Ischemic	101	Basal ganglia, internal capsule, and Corona radiata /Left	3	0	3
11	71/M	Ischemic	41	Basal ganglia and parietal lobe/Left	1	25	3
12	56/M	Ischemic	38	Insula cortex , temporal and parietal lobe /Left	3	0	3

Abbreviations: M, Male; F, Female; L, Left; R, Right; NIHSS, National Institutes of Health Stroke Scale; MAS, Modified Ashworth Scale.

Table 3. Metabolic Profiles of HIIT and MICE Protocols

n=12	HIIT (SD)	MICE (SD)	P-VALUE
Average VO ₂ (L/min) #	1.17 (0.30)	1.09 (0.26)	0.055
Average VCO ₂ (L/min) #	0.95 (0.26)	0.85 (0.22)	*0.014
VE (L/min) #	32.23 (7.01)	29.30 (6.58)	*0.003
TV (L) #	1.17 (0.45)	1.12 (0.33)	0.241
BF (breaths/min) #	28.31 (5.61)	26.56 (5.35)	0.201
Average HR (bpm) †	102.75 (10.76)	101.97 (9.35)	0.732
Peak HR (bpm) †	114.98 (12.07)	105.97 (8.81)	*0.036
EE (kcal/min)	115.16 (21.73)	107.34 (2.63)	0.203

Abbreviations: VO₂, volume of oxygen consumption; VCO₂, volume of carbon dioxide production; V_E, minute ventilation; TV, tidal volume; BF, breathing frequency; HR, heart rate; EE, energy expenditure. * p <0.05. #, two participants incomplete due to equipment malfunction; †, five participants incomplete due to equipment malfunction.

Table 4. Transcranial Magnetic Stimulation Measures Before and Following HIIT and MICE

TMS Measure (HIIT)	Affected Hemisphere		Less Affected Hemisphere	
	Pre (SD)	Post (SD)	Pre (SD)	Post (SD)
SICI (% of Unconditioned MEP)	13.3 (12.7)	15.8 (22.8)	25.2 (14.9)	32.1 (22.04)
ICF (% of Unconditioned MEP)	17.2 (19.2)	24.9 (28.8)	35.5 (28.8)	46.2 (44.9)
RMT (MSO %)	58.3 (29.9)	59.5 (30.9)	45.6 (8.1)	45.3 (11.1)
TMS Measure (MICE)				
SICI (% of Unconditioned MEP)	11.6 (13.5)	11.6 (13.7)	22.03 (11.1)	30.5 (20.6)*
ICF (% of Unconditioned MEP)	23.2 (38.4)	22.7 (29.7)	33.3 (23.8)	39.2 (31.05)
RMT (MSO %)	60.9 (26.4)	60.3 (27.1)	43.5 (8.2)	42.1 (6.7)

Abbreviations: SICI, Short interval intracortical inhibition; RMT, Resting motor threshold; ICF, Intracortical facilitation. * Significantly different from pre-values, $p < 0.05$.

Effects of Exercise on Intracortical Networks

Short Interval Intracortical Inhibition. Pre exercise SICI was greater in the more affected hemisphere compared to the less-affected hemisphere ($t(23) = -2.903$, $p = 0.008$, 12.47 % (12.92) vs 23.62 % (13.01)). Across the three different ISI tested there were no difference in SICI values so we collapsed the SICI values. SICI measures in the less affected hemisphere showed a significant main effect of time ($F_{1,11} = 6.331$, $p = 0.020$, $\eta_p^2 = 0.223$), but no significant interaction with effect of time x exercise intensity ($F_{1,11} = 0.063$, $p = 0.804$). To further evaluate the effect of time in the two groups, we compared

pre values to post values in MICE and HIIT separately. After MICE, in the less affected hemisphere, SICI values significantly decreased, 22.03 % (11.14) to 30.5 % (20.63) (Figure 3, Panel A, $p=0.040$, CI -16.592 – -0.447) whereas in the HIIT group there was no significant change 25.22 % (14.97) to 32.19 % (22.04) ($p=0.186$, CI -17.864 – 3.912). In the more affected hemisphere, there was no main effect of time ($F_{1,11} = 0.246$, $p=0.625$) and no effect of time x exercise intensity (Figure 3, Panel B, $F_{1,11} = 0.256$, $p=0.618$).

Intracortical Facilitation. There was no significant change in ICF following either of the AE methods. In the more affected hemisphere there was no main effect of time ($F_{1,11} = 0.625$, $p=0.438$) and no interaction of time x exercise intensity ($F_{1,11} = 0.806$, $p=0.379$). Also, there was no main effect of time ($F_{1,11} = 3.848$, $p=0.063$) and no effect of time x exercise intensity ($F_{1,11} = 0.320$, $p=0.577$) in the less affected hemisphere.

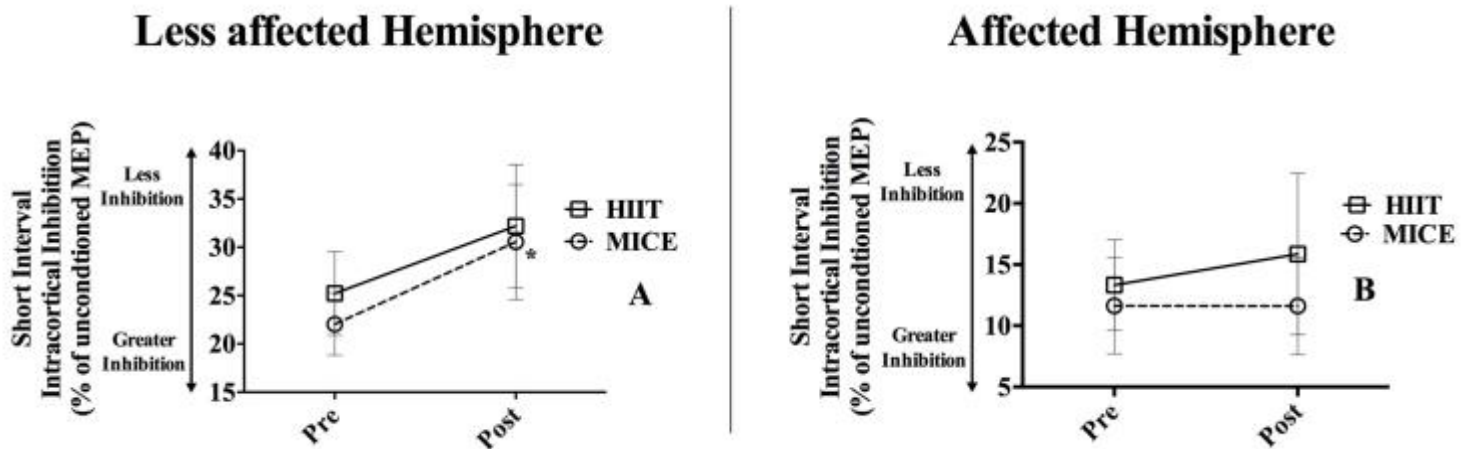


Figure 3. The effects of high intensity interval training and moderate intensity continuous exercise on short interval intracortical inhibition in the affected and less affected hemispheres. Following MICE, SICI was significantly decreased in the less affected hemisphere (22.03 % (11.14) to 30.5 % (20.63), $p=0.040$, CI -16.592 – -0.447) A, but not the affected hemisphere B. * Significantly different from pre-value, $p < 0.05$. Error bars represent standard error of the mean.

Effects of Exercise on Resting Motor Threshold

As expected, pre-exercise at rest RMT was significantly higher in the affected hemisphere compared to the less affected hemisphere ($t(23) = 2.956$, $p = 0.007$, 59.62 MSO % (27.67) vs 44.58 MSO % (8.06)). In the less affected hemisphere there was no main effect of time ($F_{1,11} = 0.642$, $p = 0.432$) and no significant interaction in the effect of time x exercise intensity ($F_{1,11} = 0.231$, $p = 0.636$), 59.62 MSO % (27.67) to 59.91 MSO % (28.50). Furthermore, in the affected hemisphere, there was no main effect of time ($F_{1,11} = 0.098$, $p = 0.757$) and no effect of time x exercise intensity ($F_{1,11} = 0.882$, $p = 0.358$), 44.58 MSO % (8.06) to 43.75 MSO % (9.16).

Effects of Exercise on Hand Function

The hands were not engaged in the exercise activity yet there were effects of exercise on hand function. Pinch strength measures in the less affected hand showed no main effect of time ($F_{1,11} = 2.155$, $p = 0.156$) and no time x exercise intensity interaction ($F_{1,11} = 0.426$, $p = 0.521$). In contrast, pinch strength in the affected hand showed both a main effect of time ($F_{1,11} = 11.705$, $p = 0.002$, $\eta_p^2 = 0.347$), and a significant interaction effect of time x exercise intensity ($F_{1,11} = 4.663$, $p = 0.043$, $\eta_p^2 = 0.179$). Pinch strength significantly decreased from 6.31 kg (5.0) to 5.85 kg (4.71) (Figure 4, $p = 0.009$, CI: 0.136 – 0.776) following MICE, while there was no significant change in pinch strength 6.37 kg (5.63) to 6.27 kg (5.51) ($p = 0.197$, CI: -.062 – 0.270) following HIIT.

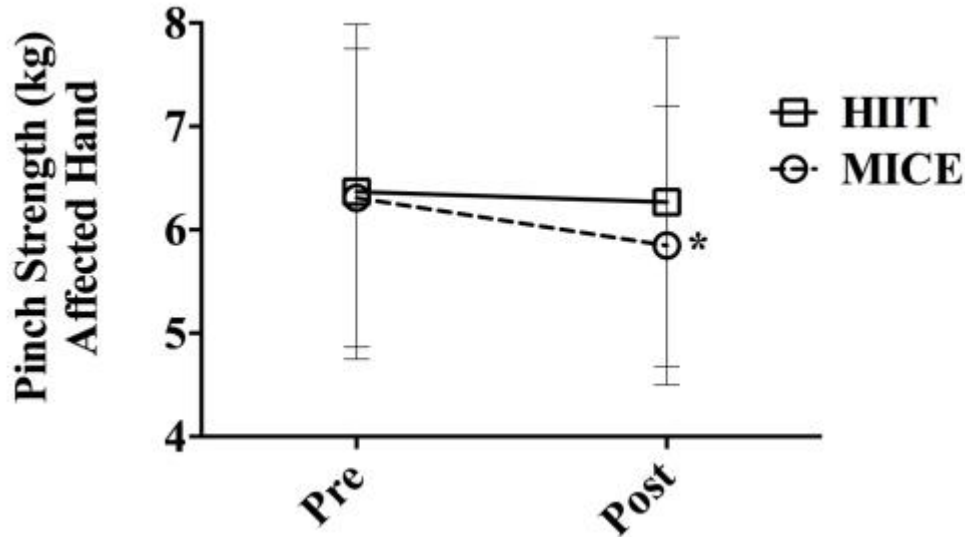


Figure 4. Change in pinch strength of the affected hand after aerobic exercise. Pinch strength in the affected hand was significantly decreased following MICE ($F_{1,11} = 1.814$, $p = 0.043$), but not HIIT. * $p < 0.05$. Error bars represent standard error of the mean.

Grip strength in the affected hand showed no main effect of time ($F_{1,11} = 0.125$, $p = 0.727$) and no interaction effect of time x exercise intensity ($F_{1,11} = 0.195$, $p = 0.663$). Also, in terms of the grip strength of the less affected hand, there was no main effect of time ($F_{1,11} = 0.002$, $p = 0.967$) and no interaction effect of time x exercise intensity ($F_{1,11} = 0.210$, $p = 0.651$).

In terms of manual dexterity (BBT) there was no main effect of time ($F_{1,11} = 0.202$, $p = 0.657$) and no interaction effect of time x exercise intensity ($F_{1,11} = 1.189$, $p = 0.191$) in the affected hand. In the less affected hand there was no main effect of time ($F_{1,11} = 1.237$, $p = 0.278$) and no interaction effect of time x exercise intensity ($F_{1,11} = 0.704$, $p = 0.411$).

Relationship between Excitatory/Inhibitory Networks and Hand Function

After MICE, SICI change score in the affected hemisphere was associated with pinch strength change score in the affected hand. (Figure 5, $r = -0.665$; $p < 0.05$). All other correlations were not statistically significant ($r \leq 0.415$, $p \geq 0.180$).

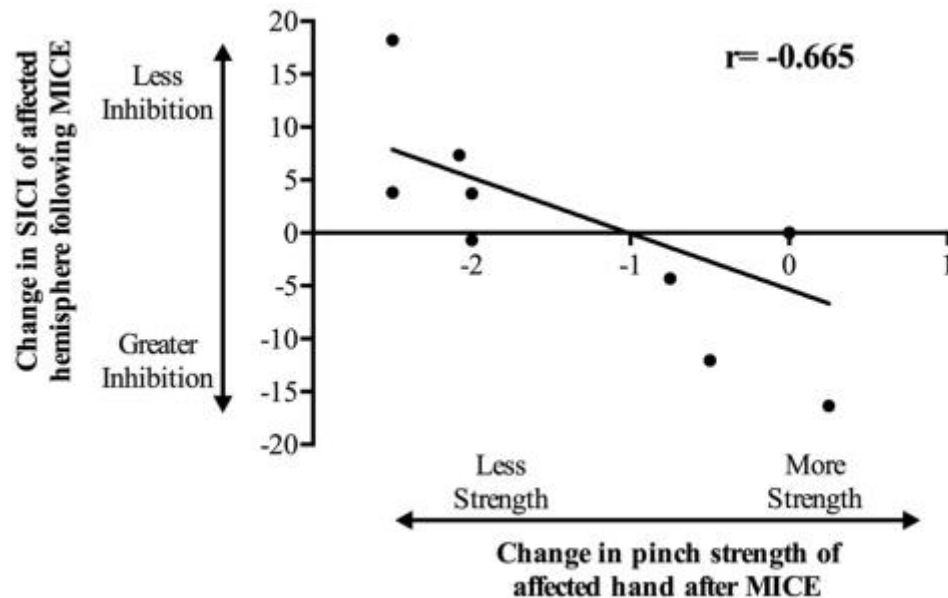


Figure 5. Relationship between short interval intracortical inhibition (SICI) measures and pinch strength. Following moderate intensity continuous exercise, greater SICI in the affected hemisphere was related to greater pinch strength in the affected hand. $r = -0.665$; $p < 0.05$.

Discussion

This study sought to determine which type of AE (HITT or MICE) would influence cortical excitability among people with chronic stroke. Moderate continuous AE appears to influence the cortical networks in the stroke brain more than HITT. We also investigated whether there was a relationship between post-exercise changes in neural networks and changes in hand function. The main findings of this study were that:

- 1) MICE reduced SICI in the less affected hemisphere, with no effects in the more affected hemisphere
- 2) there was no change in ICF or RMT within either hemisphere

following either HIIT or MICE. We also found that SICI in the affected hemisphere after MICE (but not HIIT) was associated with pinch strength of the affected hand.

Inhibitory Effects of MICE

We observed that MICE reduced SICI only in the less affected hemisphere, which aligns with previous findings in healthy individuals demonstrating that moderate intensity cycling decreased inhibition in the M1.^{111,114} SICI is believed to act through GABA- α receptors^{185,186} and the fine tuning of GABA mediated inhibitory networks plays an integral role in the induction of neuroplasticity in cortices and throughout the brain.^{187,188} In stroke populations, it is thought that a reduction in SICI may have a role in functional reorganization of both hemispheres.^{174,189} AE is postulated to downregulate GABA synthesis¹⁹⁰ and our observation of lower inhibition suggests reduced GABA activity. Thus, a decrease in GABA could result in enhanced neuroplasticity.¹⁸⁷ As a result, the current study illustrates that continuous AE can modulate cortical networks that influence descending motor outputs in chronic stroke patients.

MICE primarily challenges the aerobic energy system.¹⁹¹ Long term engagement (>6 months) in MICE leads to improved cardio-respiratory fitness and physiological adaptations such as: increased blood volume, capillary density, and increased mitochondrial size.¹⁹¹ Continuous AE in rodents leads to greater hippocampal neurogenesis compared to HIIT and resistance training.¹⁹² Aerobic exercise is believed to mediate its positive effects through BDNF an important neurotrophic factor for synaptic plasticity, learning, memory, and cognitive enhancement.^{113,193} Ploughman *et al.*, 2005¹⁹⁴

observed that rats with focal ischemia performing one bout of moderate continuous exercise experienced a greater increase in BDNF compared to higher intensity training. In another study rodents that lacked BDNF expression experienced poor recovery, which highlights the importance of BDNF for recovery.¹⁶⁹ Summarising, MICE appears to exert positive benefits on the brain by upregulating BDNF and creating an environment for neural growth that could benefit stroke patient recovery.

In addition, we observed that stroke patients performing MICE on a recombinant stepper, (without their hands engaged), experienced a change in neural networks (inhibition) of the non-exercised FDI muscle. This aligns with previous research in which healthy individuals following moderate intensity lower limb cycling activity, showed changes in cortical excitability of the upper limb.^{111,114,195} One suggested explanation is that AE causes a spreading effect of excitability from the exercised muscle to adjacent M1 areas of non-active muscles.^{114,196}

Another important component of our study was that we matched each exercise session for total EE, which is a consideration often overlooked. Each exercise session was matched for total amount of work performed. This enabled us to evaluate the effect of AE intensity as opposed to other exercise parameters such as duration of exercise. Furthermore, matching the exercise sessions strengthens our conclusions about how the intensity of AE influences the neural networks. Future studies should consider matching for EE when comparing two effects of different exercise training methods. It is likely that once a certain threshold of intensity is met (moderate), duration rather than intensity becomes the primary driver of cortical network changes.

There was no change in ICF in either hemisphere following HIIT or MICE. We were not able to successfully activate facilitatory networks mediated through glutamatergic interneurons and N-methyl-D-aspartate receptors.^{197,198} Since MEPs generated with ICF were less than that of the test stimulus (<100 %), we speculate inhibition rather than facilitation took place (Table 3). Previous research among healthy individuals has shown that AE causes increased ICF.^{111,114} Our findings are contrary to previous work by Blicher *et al.*, 2009 and Liepert *et al.*, 2000 who were able to collect ICF in a relaxed hand muscle (abductor pollicis brevis and FDI) before and after a training task.^{168,199} These studies used an ISI of 10ms and 15ms, while we used an ISI of 12ms. Thus, the ISI we used may not have been optimal to elicit ICF in the altered networks of the brain affected by stroke.

AE Effects on Corticospinal Excitability

Corticospinal tract excitability (CSE) is thought to represent the summation of inhibitory and excitatory inputs on descending neurons.²⁰⁰ The size of MEP are used to quantify the level of excitability within the corticospinal tract. Previous work suggests that increasing the excitability of the affected hemisphere through non-invasive brain stimulation leads to improved motor skill acquisition²⁰¹ and motor function²⁰² in stroke patients. We found that there were no changes in CSE following HIIT or MICE. These findings align with previous work by Singh *et al.*, 2014 and Neva *et al.*, 2017, who showed that healthy individuals performing a single bout of moderate intensity cycling for 20 minutes^{114,195} displayed no changes in CSE. Also, stroke patients engaging in a

single bout of treadmill HIIT training showed no changes in CSE.²⁰³ It could be that AE may not be sufficiently focal to directly affect the corticospinal tract of the affected hand. As expected, we observed higher pre-exercise RMT in the affected hemisphere compared to the less affected hemisphere. This observation is supported by a meta-analysis that showed corticospinal excitability is lower in the affected hemisphere than the less affected hemisphere following stroke.²⁰⁴ We anticipated that AE would have increased CSE, comparable to motor training²⁰⁵, but we saw no change.

MICE Effect on Pinch Strength

Previous research among people with stroke has shown that decreasing inhibition of the affected hemisphere through non-invasive brain stimulation leads to better function in the paretic hand.²⁰⁶ In our study, we observed a somewhat unexpected finding in that there was *decreased* pinch strength in the affected hand following MICE, but not HIIT. This finding contradicts Ploughman *et al.*, 2008 who reported that stroke patients following treadmill exercise improved hand function, which was measured by the Action Research Arm Test.¹⁷⁷ Previous literature suggests that AE lowers inhibition in M1.^{111,114} In mice, decreasing inhibition in the lesioned hemisphere is linked to improved functional recovery.²⁰⁷

We also observed that greater inhibition of the affected hemisphere was related to *increased* pinch strength after MICE. Taken together, these disparate findings may suggest that in this group of chronic stroke patients with wide ranging hand impairments (from 0-37 kg of grip strength) the more affected hemisphere may be contributing less to

hand movement. The relationship between greater inhibition in the affected hemisphere and enhanced post-exercise pinch strength suggests that for some patients pinch strength is being mediated by regions other than contralesional M1. This suggests that in some patients inhibiting rather than facilitating the affected hemisphere has a greater benefit. Our sample size was too small to split the group by impairment level but the effects of AE among people with varying limb impairment is an important area for future research.

Another possible explanation could be spasticity, which causes development of excessive activation of flexor muscles²⁰⁸ of the impaired hand due to lost input from supraspinal areas disrupting the balance of inhibition and facilitation.^{42,208} AE may have relaxed spasticity in the hand making it appear that pinch strength decreased when perhaps spasticity-facilitated flexion was reduced. Thus, MICE may have rebalanced supraspinal imbalance in stroke patients leading to decreased spasticity and greater finger control. As mentioned, assessing the effects of AE on varying levels of hand impairment may help uncover differing neurophysiological effects of AE.

Limitations

Although this study is the first to compare the effects of HIIT and MICE on CSE and intracortical networks, there are some limitations. Firstly, we had great variability in our TMS measures and severity of stroke among participants. We deliberately chose a heterogeneous group to better understand AE's effects in a typical stroke population. However future work could involve recruiting an equal proportion of mildly and severely affected patients. Secondly, we also attempted to measure transcallosal inhibition but

were unable to obtain clear ipsilateral silent periods. Obtaining the transcallosal inhibition measure may have enabled us to provide more conclusive data regarding how the less affected hemisphere may have influenced the affected hemisphere following AE.

Conclusion

In summary, moderate continuous AE appears to influence the cortical networks in the stroke brain more than HIIT. The inhibition in the less affected hemisphere was decreased following MICE (GABA mediated) in chronic stroke patients while the inhibition in the affected hemisphere remained the same. This may suggest that MICE training can modulate inhibition in intrahemispheric networks in the less affected hemisphere and future work should explore the role of less affected hemisphere modulation in influencing recovery and motor function following stroke.

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Chapter 3: Discussion

The purpose of conducting this study was to compare the effects of two different types of AE (continuous vs interval) on brain excitability in chronic stroke patients. Based on previous research, we hypothesized that HIIT may provide a more intense stimulus to the chronic stroke brain, creating an environment where use-dependent plasticity could be more readily promoted.^{115,209,210} Stroke is a leading cause of death and disability worldwide,^{19,18} and impacts many aspects of daily functioning,^{30,32-34} however motor impairments are one of the most pervasive and debilitating consequences of stroke. These impairments require ongoing innovative therapies, particularly once people transition into the chronic phase. This study aimed to better understand the dose of AE required to foster plasticity in people with chronic stroke.

In this chapter, the discussion presented in chapter two will be expanded upon to demonstrate how our study answered the primary research questions. In addition, strength and limitations of the study will be explored in depth and finally, future directions will be discussed.

The Impact of Aerobic Exercise Intensity in Changes to Intracortical Inhibitory and Facilitatory Networks in Chronic Stroke

Findings from our study suggest that an acute bout of MICE impacts intracortical inhibitory networks in people with chronic stroke. AE is thought to influence the brain by down regulating the inhibitory GABAergic system, while also upregulating the excitatory glutamatergic system.¹⁹⁰ It is well established that a decrease in GABA is important for motor learning and M1 plasticity.²¹¹ Horizontal connections exist within M1, which play a key role in activity-dependent plasticity.⁵⁴ A reduction in inhibitory signalling is believed to unmask

horizontal connections that results in changes in motor map representations.²¹² Our findings suggest that an acute bout of MICE can act as a focal stimulus to alter the inhibitory networks in the M1 of chronic stroke patients. Compared to HIIT, we observed that following MICE there was less inhibition in the less affected hemisphere, while there was no change in the affected hemisphere.

Our study is the first to compare the effects of two different AE methods on inhibitory networks in M1 of stroke patients. The reduced SICI described in this study was similar to that described in healthy volunteers whom after a single 20 minute moderate intensity cycling activity demonstrated a decrease in SICI (less inhibition).¹¹⁴ Smith *et al.*, (2014) also demonstrated that, following an acute bout of 30 minutes of cycling at either 40 % intensity or 80 % intensity, healthy individuals experienced a transient reduction in the level of M1 inhibition.¹¹¹ Following stroke, damage in the affected hemisphere leads to a disrupted inhibitory system, compromised of transcallosal signalling between the hemispheres.²¹³ It is believed that the unaffected, less affected hemisphere exerts a greater amount of inhibition on the affected hemisphere that leads to asymmetric transcallosal inhibition following stroke.^{159,214} Therefore, it is reasonable to think that a decrease in inhibition (as seen during MICE in our study) may facilitate greater recovery post-stroke. It has been shown that exercise improves arm function following stroke,²¹⁵ and individuals with greater decreases in M1 GABA displayed greater motor learning.²¹¹ Therefore, identifying MICE as a potential intervention to modulate brain networks in a chronic stroke population provides evidence for the brain's continued malleability in the chronic phase of stroke and has important implications for stroke rehabilitation, which will be touched upon further in the future directions section of this chapter. Since decreased inhibition is necessary for induction of long term potentiation plasticity in M1, MICE shows promise for

altering plasticity and enhancing motor recovery even among those with chronic stroke who are thought to have moved beyond the “window of plasticity” of 3-6 months.⁴⁴

Based on our findings, AE did not appear to influence excitatory networks in chronic stroke, however this finding should be interpreted with some caution. Intracortical facilitation (ICF) networks are excitatory networks believed to be mediated through glutamatergic interneurons and NMDA receptors.¹⁹⁷ In healthy individuals, following a bout of AE there is increased facilitation in the brain, which is believed to play a role in altering synaptic strength.¹¹⁴ We were not able to induce facilitated MEP in our study sample. As previously discussed, our results appear to show inhibition, which differs from previous findings that have shown ICF in stroke patients¹⁹⁹, and changes in ICF in healthy individuals.¹¹⁴ Our inability to activate facilitatory networks among study participants may have been related to the inter-stimulus interval (ISI) employed. We chose 12ms¹¹⁴ as our ISI, however ISIs range from 10-25ms.¹⁵⁶ Therefore, for individuals with chronic stroke, due to the heterogeneity of impairments, we may have chosen an ISI that was possibly too short to activate these networks. ISI may be highly specific to the clinical population of interest. However, our results suggest that ICF is simply more difficult to elicit in people with chronic stroke, likely due to altered intracortical networks. Following stroke there is damage to the brain and distinct differences between hemispheres develop. The variability of each stroke makes it more difficult to use one protocol for everybody. Furthermore the differences between subcortical and cortical stroke may influence neurophysiological measures differently. Therefore, it appears that our inability to detect changes in ICF may be attributed to the current testing protocol and may not truly reflect whether AE is an appropriate stimulus to activate facilitatory networks among people with chronic stroke.

The Effects of Different Acute Aerobic Exercise Intensities on Excitability of the Corticospinal Tract in Chronic Stroke

As mentioned, our findings suggest AE does not impact overall excitability of the corticospinal tract in people with chronic stroke. Resting motor threshold (RMT) is used to assess the integrity of the corticospinal tract and observe changes in corticospinal excitability (CSE). Lower RMT is indicative of greater CSE, while higher RMT indicates less CSE. In our study, there was no difference in RMT following either HIIT training or MICE training. This observation aligns with similar reports that examined the effect of AE on cortical excitability in healthy individuals.^{111,114,195} For example, following moderate exercise intensity, continuous cycling in healthy individuals, Smith *et al.*, (2014) observed no change in corticospinal excitability of the FDI hand muscle.¹¹¹ In accordance, Neva *et al.*, (2017) also showed, following lower limb cycling at a moderate intensity, there was no change in corticospinal excitability or spinal excitability in young, healthy adults.¹⁹⁵ In a chronic stroke population it was observed that there was no change in corticospinal excitability following a single session of HIIT on a treadmill.²⁰³ It appears that exercise can influence specific intracortical inhibitory networks, but has less impact on overall corticospinal excitability. However, this present study was the first to compare the effects of MICE and HIIT on CSE among chronic stroke patients and we showed similar responses after AE as in healthy adults; contributing uniquely to our understanding of the effects of acute aerobic exercise intensity on overall excitability of the corticospinal tract in chronic stroke.

Since RMT did not change following AE at either intensity, this may suggest that the overall corticospinal system was not affected, however, the effects may have been on individual components of the circuitry. The amount of cortical activity is dependent on axonal threshold

and excitability of cortical neurons.²¹⁶ There are also connections between the cortex and corticospinal tract in the spinal cord (SC), and synapses between the SC and the motor neurons at the muscle level.²¹⁶ Therefore, future research should not only probe corticospinal excitability, but should consider the effects of AE on excitability of the spinal circuitry. Changes in excitability of the spinal circuitry may provide a better understanding of how different components of the corticospinal tract system interact and are influenced by AE.

In the chronic phase of stroke, previous research suggests there is an uneven level of CSE between the affected and less affected hemispheres.²⁰⁴ Our findings confirm that this difference in RMT between hemispheres exists. At baseline, the affected hemisphere demonstrated lower CSE (greater RMT) compared to the less affected hemisphere. Reduced CSE is associated with poor hand function.²¹⁷ It has been shown that ipsilesionally, there is less corticomotor excitability, and the degree of motor recovery post-stroke is dependent on the increase of ipsilesional corticospinal activity.¹⁷² In the present thesis, we had hypothesized that HIIT would provide a more intense stimuli to increase excitability in the brain, but it appears that there was no effect of AE on CSE. Moving forward, pairing AE with another task should be investigated, as it has been shown that pairing exercise with motor learning tasks can lead to greater changes in excitability. This point will be expanded upon in the future directions section of this chapter.

The Impact of Aerobic Exercise Intensity on Changes in Functional Outcome Measures in Chronic Stroke

Fine Motor Function

Following stroke, the activity of M1 in the affected hemisphere is disrupted, which results in impaired execution of voluntary movements. Throughout the recovery process,

increasing the excitability of the affected hemisphere improves motor function.^{75,218} Pinch strength is a clinical measure believed to reflect motor strength and level of hand paresis.^{148,219} Following the two AE intensities used in our study, there was a greater decrease in pinch strength following a bout of MICE compared to HIIT. The execution of unimanual and bimanual movement, such as the pinch strength test, requires communication between M1s in each hemisphere.²²⁰ Disrupted transcallosal signalling is associated with impaired motor output and reduced motor function in individuals with stroke.^{214,221} Among individuals with chronic stroke, removing inhibition following MICE may have a counterintuitive effect on the brain. The neural circuitry of the recovered brain adapts to execute movements with an increased level of inhibition in the affected hemisphere. Lowering inhibition in the less affected hemisphere, as observed by our SICI findings following MICE (Figure 3), may have manifested as acute poorer motor function and decreased pinch strength. Interestingly, this finding was specific to our fine motor measure of strength as we did not observe a change in gross motor strength or dexterity as indicated by the lack of differences in grip strength and BBT following AE. Therefore, this disruption appears to affect neural circuitry responsible for pinch strength specifically compared to gross motor control. As this finding was not observed following HIIT, fine motor strength was not affected when individuals performed high intensity exercise with intermittent bouts of rest. However, due to the known effects of rehabilitation interventions on restoring this imbalance between hemispheres, longer term AE exposure paired with skilled training has the potential to yield greater motor recovery. Therefore, more research is needed to compare short versus long-term effects of AE intensities on motor function and strength following stroke.

Fine Motor Function and Intracortical Inhibition.

Following a bout of MICE, greater inhibition in the affected hemisphere (SICI) was associated with stronger pinch strength in the affected hand (figure 5). Stated another way, individuals with greater intracortical inhibition in the less affected hemisphere had increased force output on pinch strength test. This finding is counterintuitive as it indicates that more inhibition in the affected hemisphere leads to greater motor strength in the affected hand. This is in direct contradiction of conclusions drawn from transcranial direct stimulations studies in which it was shown that increasing the excitability of the affected hemisphere leads to improved function on a motor task.^{202,206} A possible explanation for the changes in pinch strength we observed is that there could be another related mechanism controlling motor output such as spasticity. Decrease in pinch strength may represent release of spasticity due to excessive activation of the corticospinal tract controlling flexor muscles in the hand.

The progression of motor recovery following stroke coincides with the presentation and resolution of spasticity.²⁰⁸ Spasticity is believed to be caused by aberrant plasticity that leads to excessive muscle activity and hyperreflexia.²²² Decreasing spasticity in stroke patients would reduce the rigid movement of the thumb and index finger involved in the pinch strength task. Greater tone can sometimes be mistaken for greater strength when executing a fine pinch task, since people recruit agonist and antagonist muscles, which are involuntary contracted to execute the desired movement.²²³ Following AE, alterations in the brain may lead to lower tone which would lead to a lower pinch strength. This lower strength, like the one we observed in our findings, may indicate that greater fine motor control is available because desired muscle groups can be activated as opposed to activation of non-related muscles to execute a pinch task. When designing future studies, we should attempt to use more sensitive measurements that delineate

the effects of spasticity and can detect small changes in function. The role of spasticity and the influences of AE on spasticity is an area ripe for future research since spasticity is a major impediment to skillful movement.

Cortical Excitability and Clinical Measures

We also collected grip strength and the BBT. These measures assess gross motor strength²²⁴ and manual dexterity¹⁴⁶ respectively, of the paretic hand. Improvement in strength has been shown to be linked to greater recovery in the affected limb in stroke patients.²²⁵ Our study found no difference in grip strength and BBT measures pre- and post-exercise, after either AE condition. In addition, no correlation was observed in the affected or unaffected hemispheres between TMS measures and grip strength and BBT. However, a previous study with stroke patients performing treadmill-based AE observed an improvement in walking related measures, such as stride length and walking speed.²⁰³ This is perhaps not surprising considering that the lower extremities are employed as part of the training program. The authors suggested that these improvements were related to improved aerobic capacity as opposed to alterations in cortical activity. We did not test gait parameters in the present study, and therefore we are limited to interpreting the effects of AE intensities on the upper limb.

Based on findings from Hasan *et al.*, 2016 systematic review,¹¹⁹ AE does not appear to consistently improve upper limb function, but facilitates the improvement of functional outcomes when paired with skilled training. In the present study, we did not observe an influence of AE on functional outcomes, such as grip strength or BBT, however, we did not pair exercise with skilled training. To prime the brain, and facilitate the motor recovery process post-stroke, the combination of AE and skilled training may be essential. Further research comparing different AE intensities paired with skilled training in individuals with chronic stroke is needed.

Strengths and Limitations

Our study was the first of its kind to compare the effects of two different AE methods on the neural circuitry in a stroke population. We hoped to contribute to the field of stroke rehabilitation research by providing evidence for the appropriate AE intensity for stroke patients, to maximize plastic responses in the brain. The study design also attempted to establish TMS methodological protocols for assessing inhibitory networks in the brain. By testing different ISIs we could determine if different lengths of ISI produced different results, and if this translated to changes in the inhibitory responses we observed. We saw that between 2ms, 2.5ms and 3ms there was no difference in the SICI value. Being able to methodically test each ISI allows us to make recommendations about which ISI to use to elicit the greatest amount of inhibition and establish a protocol that can be used in future studies, and should be seen as a strength in the present study.

A second methodological issue that was addressed in this study was matching the workload in each exercise session for total EE. Little consideration in the existing literature is given to standardizing AE sessions for total work. The aim of matching EE was to ensure that in both conditions, despite differences in target HR (intensity) participants were performing the same amount of work. If there were any changes seen in the brain networks it would be due to peak intensity of the AE session and not other factors, like total exercise time. This method of controlling the delivery of the training paradigm also gives us more confidence in the conclusions we make about AE intensity's effects on the brain affected by stroke.

There were also several limitations in this study. Although we used a crossover design to partially address issues regarding the small sample size and issues of heterogeneity among participants, this was still a limitation of the study. We had originally aimed to recruit 17

participants but were only able to recruit 13, and had to exclude one participant from our analysis because they received an official diagnosis of Parkinson's disease during the study, reducing the final sample size to 12. Having a small sample reduces our ability to generalize and make definitive conclusions about the benefits of targeting AE intensity for recovery in chronic stroke. Nevertheless, this study was still able to contribute to our understanding of how different AE intensities impact the brain in chronic stroke, laying the ground work for a larger randomized control trial with an appropriate sample size and healthy controls to further tease out the effects of AE intensity on the neural circuitry in people with chronic stroke.

As previously mentioned, our participants represented a heterogeneous population of stroke patients with varying levels of disability. Inclusion criteria required participants to ambulate on their own, but individuals still presented with varying degrees of hemiplegia and noticeable walking impairment. We did not limit our sample to high functioning individuals with the hope of capturing a wide range of stroke patients, but in doing so we increased the variability of our sample and this may have contributed to wide standard deviations and lack of significant differences we observed in our findings.

Transcallosal inhibition (TCI) was a variable of interest in our study, it measures the activity of callosal fibers which pass through the corpus callosum connecting M1 in each hemisphere.²²⁶ We were not able to detect any definitive silent period with any consistency, which hindered our ability to report this measure. Successfully collecting this measure may provide key insight into the role of hemispheric balance of inhibition in the chronic stroke brain. The decrease in inhibition of the less affected hemisphere is assumed to translate into less inhibition from the affected hemisphere. This is deduced from our understanding of brain circuitry in that following rTMS, it has been shown that downregulating activity of one

hemisphere leads to the upregulation of activity in the other hemisphere.²²⁷ Without a TCI measure we are unable to make definitive conclusions. The study protocol may have been inappropriate, in that we may have used too large of an MVC and not an appropriate suprathreshold stimulus. To overcome these errors, pilot work needs to take place in order to test different TCI protocols and identify what works best in a stroke population when collecting the TCI measurements. Moving forward, future studies should collect TCI measures when attempting to characterize the inhibitory networks in the stroke brain.

Future Directions

Exercise Intensity and Best Practices for Chronic and Acute Stroke

The present study probability of the brain post-stroke. In the present thesis, our research suggests that MICE modulates cortical excitability more than HIIT. The use of F.I.T.T. (frequency, intensity, time and type of exercise) principles when designing exercise programs is important for establishing dose-response effects and provides information about the intervention's effectiveness.¹³⁵ It has been suggested that F.I.T.T. principles should be considered when implementing AE in stroke rehabilitation, to ensure that the effects of AE are maximized.¹³⁶ Currently F.I.T.T. components are used to determine a physical training program's effect on cardiorespiratory fitness, muscular strength and endurance.¹³⁵ Our study suggests that F.I.T.T. components are also important to consider when cortical excitability is the outcome. Going forward, to enhance best practice guidelines, studies should also investigate several types of training protocols at the acute stroke phase. This phase of stroke recovery (< 3 months) is the most optimal window of recovery where a cascade of changes that lead to spontaneous neural recovery. Designing AE therapies specific to the stage of recovery is important so that patients can experience the greatest level of recovery possible.

Pairing Exercise with Additional Interventions to Enhance Neurorehabilitation

In addition to developing a clearer picture of how AE intensity affects the brain in the acute and chronic phases of stroke recovery in order to inform best practice, several issues remain surrounding how to most effectively incorporate AE into neurorehabilitation. Pairing exercise with additional interventions to examine its additive effects on neuroplasticity is one such area. Interestingly, while AE has been shown to increase the number of neurons created in the hippocampus in mouse models, environmental enrichment is necessary for the newly formed neurons to survive and incorporate into existing neural networks.^{228,229} These models suggest that the combined effect of AE and environmental enriched living may further the post-stroke recovery processes. Therefore, future studies should investigate whether changes following exercise at moderate and high intensities are differentially influenced when individuals with stroke are exposed to periods of environmentally enriched living.

Furthermore, new neurons created over the course of AE have been shown to die if inadequate learning opportunities or novel experiences do not accompany them.^{229,230} This points to the potential for research to explore pairing AE with other task specific therapies. In the present study, we assessed changes in functional motor tasks immediately following bouts of exercise, however, future studies could focus on the effect of exercise protocols using HIIT and MICE on long-term, task-specific upper extremity motor practice in post-stroke recovery. Following AE, the brain appears to become more plastic. Taking advantage of this environment by pairing task-specific practice could increase the likelihood of maintenance of new neuron formation. It has been shown that in healthy individuals, pairing AE with the learning of a motor

task encourages skill acquisition and modulates the motor pathways.²⁰⁹ However, few studies have investigated the differential effects of AE intensities on long-term motor skill practice and learning in individuals with chronic stroke. Interventions like robot-assisted movement^{80,231} training and bimanual training^{82,83} have been shown to improve motor function; pairing these techniques with different intensities of AE may enhance their positive effects and lead to even greater improvements. If AE provides an optimal environment for neuroplasticity, this would support the implementation of AE before task specific therapies in stroke rehabilitation.

Understanding the Mechanisms that Drive Neuroplastic Change.

Following our observation that continuous AE influences cortical excitability by decreasing inhibition in intracortical networks, there should be a call to capitalize on its potential use in stroke rehabilitation.⁸ It is understood that AE can modulate M1 and influence neuroplasticity.⁸ Additionally, it is known that AE plays a role in creating an environment where neuroplasticity is encouraged.^{104,232} As discussed in chapter 2, BDNF is a neuronal growth factor implicated in the role of neuroplasticity following AE.^{233,234} It has been shown that rats who have downregulated levels of BDNF have limited recovery following stroke and have poor long-term prognosis.¹⁶⁹ In humans, there are individuals with BDNF polymorphisms, Val66Met, that causes decreased BDNF secretion during activity.²³⁵ Those with the BDNF polymorphisms have been shown to have decreased motor map reorganization and M1 excitability following a motor task.²³⁶ Thus, stroke patients carrying VAL66met may not benefit from AE's role in increasing BDNF and motor rehabilitation's ability to induce motor map reorganization. However, it has been suggested that performing prolonged intense motor practise can counteract the negative effects of Val66Met on plasticity.²³⁷ Thus it is conceivable that prolonged challenging AE could

have this effect on BDNF secretion. This highlights the need for more work to be done to determine how the brain of stroke patients with or without the polymorphism are affected after chronic exposure to both types of aerobic intensity

Increasing the circulation of BDNF (via AE), to damaged cortical areas, may increase the likelihood for synaptogenesis. Acute AE may also provide a natural stimulation to the brain, jumpstarting neuronal networks that are not lost but masked due to inhibitory influences. Interestingly, Singh *et al.*, 2014¹¹⁴ and Smith *et al.*, 2014¹¹¹, showed that the changes in SICI were transient, and did not last longer than 30 minutes. Therefore, based on the findings from the present thesis, where inhibitory intracortical networks were altered, future work should consider whether prolonged exercise can cause a permanent long lasting change in the intracortical networks of the brain. Also BDNF levels in the blood should be monitored to determine if chronic AE can upregulate BDNF and whether this leads to improved function post-stroke.

Conclusion

To influence the intracortical network in chronic stroke patients, AE method matters. MICE appears to have a greater influence on the inhibitory networks of the chronic stroke brain compared to HIIT. With respect to the chronic stroke population, HIIT may not be as effective as MICE as a priming tool for the brain. Although the cardiorespiratory benefits of HIIT seemed to be unquestionable, its superiority doesn't appear to translate to its effect on the chronic stroke brain. Through our study we have been able to provide greater insight into the appropriate intensity of AE chronic stroke patients should target, which could potentially impact best practices in stroke recovery. With respect to future research directions, there should be more

work performed to determine how the brain of stroke patients are affected after chronic exposure to both types of aerobic intensity. This will help us answer whether, from a neural perspective, the changes observed are permanent and not transient.

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Appendix A

Method of calculating SICI:

$$\begin{aligned} \text{\% of unconditioned MEP} &= (\text{MEP of paired pulse stimulus } (\mu\text{V}) / \text{MEP of test stimulus } (\mu\text{V})) \times \\ &100 \\ &= (589 \mu\text{V} / 1034 \mu\text{V}) \times 100 \\ &= 56.9 \text{ \%} \end{aligned}$$

Method of calculating change score:

$$\begin{aligned} \Delta \text{ Change score} &= \text{Post measure} - \text{Pre-measure} \\ \Delta \text{ affected hand pinch grip score:} \\ &= 50 \text{ kg} - 34 \text{ kg} \\ &= 16 \text{ kg} \end{aligned}$$