Effects of Acute Aerobic Exercise on Motor Cortex Plasticity in Individuals With a Concussion History

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be electronically available to the public

Abstract

The impact of concussions was previously believed to be transient, however neurophysiological tools have revealed that long-term cognitive and motor declines persist past the acute phase of injury. Through a non-invasive brain stimulation method known as transcranial magnetic stimulation (TMS), long-term increases in gammaaminobutyric acid (GABA) mediated intracortical have been detected after sustaining a concussion. Such increases are known to suppress synaptic plasticity of the motor cortex. In healthy populations, acute aerobic exercise has the potential to enhance corticomotor excitability and intracortical networks that facilitate synaptic plasticity. This study used TMS to investigate the benefits of acute aerobic exercise on M1 plasticity in individuals with a history of concussions (>six months post-concussion). In a crossover design, participants performed a single bout of 20-minutes of moderate intensity biking, followed by a plasticity inducing method, known as paired associative stimulation (PAS), compared to PAS alone. TMS measures were collected at three time points: Pre-session, post-session one (five minutes post-PAS) and post-session two (30 minutes post-PAS). Excitability of the corticospinal networks was assessed by the motor evoked potential (MEP) and resting motor threshold (RMT). Intracortical networks that modulate cortical spinal output was measured through intracortical facilitation (ICF, 12ms), the cortical silent period (CSP), short-interval intracortical inhibition (SICI, 2ms) and long-interval intracortical inhibition (LICI, 100ms). Results demonstrated decreases in SICI in the exercise+PAS session (five minutes post-PAS), compared to the PAS alone session. MEP amplitudes increased in both the exercise+PAS session and PAS alone session. However, exercise did not further enhance the effects of PAS on MEP amplitude. No changes in CSP duration, LICI, ICF or RMT were found. Exercise-induced decreases in SICI reflect decreases in GABA-mediated inhibition, which plays a key role in

synaptic plasticity. These beneficial impacts of exercise on brain plasticity may be used as an important consideration for normalizing the long-term subclinical motor declines that persist after sustaining a concussion.

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APB – Abductor pollicis brevis

AMPA - Alpha-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid

BDNF – Brain-derived neurotrophic factor

Ca2+ - Calcium

CaMKII – Calcium/calmodulin-dependent protein kinase II

CAMP - Cyclic adenosine 3-5-monophosphate

CBF – Cerebral blood flow

CNS – Central nervous system

CS – Conditioning stimulus

CSP – Cortical silent period

cTBS – Continuous theta burst stimulation

EEG - Electroencephalogram

EMG - Electromyography

ERP – Event-related potential

FDI – First dorsal interosseous

GABA – Gamma-amino-butyric acid

GAQ – Get active questionnaire

H – Hoffmann

HPA – Hypothalamic pituitary adrenal

HR – Heart rate

HRR- Heart rate reserve

I – Indirect

ISI – Interstimulus interval

iTBS – Intermittent theta burst stimulation

K+ - Potassium

L-DOPA - Levadopa

LICI – Long-interval intracortical inhibition

LTP – Long-term potential

LTD – Long-term depression

M1 – Primary motor cortex

MEP – Motor evoked potential

ms – milliseconds

MTAT – Motor threshold assessment tool

mTBI – Mild traumatic brain injury

NMDA - N-methyl-D-aspartate

Na+ - Sodium

IPAQ – International physical activity questionnaire

PAS – Paired associative stimulation

PCSS – Post concussion symptom scoring

PKA – Protein kinase

PNS – Peripheral nerve stimulation

PP2b – Protein phosphatase 2B

RMT – Resting motor threshold

SICI – Short-interval intracortical inhibition

TMS – Transcrial magnetic stimulation

tDCS – Transcrial direct current stimulation

TrKB – Tropomyosin receptor kinase

TS – Test stimul

1.0 Introduction

Concussion is a mild traumatic brain injury (mTBI) that is defined as a "complex pathophysiological process affecting the brain, induced by biomechanical forces" (McCrory et al., 2012). Concussion has been declared a major public health concern, due to its high incidence rates and potential long-term impacts on brain function (Kelly et al., 1999). Approximately 64-74 million people sustain a concussion each year, with around half the population sustaining one or more concussions in their lifetime (Dewan et al., 2018). Acute symptoms include various functional, cognitive and/or emotional symptoms, such as a headache, nausea, vomiting, dizziness, fatigue, abnormal sleeping patterns and drowsiness. Symptoms usually resolve within 7-10 days, however symptoms persist past a month in around 1 out of 5 individuals (Dikmen et al., 2010, McMahon et al., 2014, McCrory et al., 2013). Despite the eventual resolution of symptoms there is evidence for persistent deficits even after clinical recovery. Electroencephalogram (EEG) demonstrates deficits in electrophysiological markers such as the P300 and N2 event-related potentials (ERP) in asymptomatic athletes who have previously sustained a concussion (Gosselin et al., 2006; Lavoie et al., 2004). ERP deficits are indicative of persistent subclinical alterations in attention allocation (P300) and response inhibition (N2) during sensorimotor conflict. Regarding the motor system, reductions in levels of implicit learning, slowed fine dexterity, response and movement times have been reported in asymptomatic individuals with a concussion history (De Beaumont et al., 2012; Pearce et al., 2014). These symptoms may result from direct injury to the motor cortex or from persistent altered connectivity between the prefrontal cortex and motor cortical areas months to years after the injury. Studies using

transcranial magnetic stimulation (TMS) have reported long-term subclinical motor declines in asymptomatic individuals after sustaining a concussion. This is most consistently indicated by a lengthened cortical silent period (CSP) duration, which is a measure of intracortical inhibition (De Beaumont et al., 2007; De Beaumont et al., 2009; De Beaumont et al., 2012; Lewis et al., 2017; Pearce et al., 2017; Tremblay et al., 2011). Despite persistent long-term deficits in neurophysiological function, functional deficits are rarely reported after individuals return to play (Broglio et al., 2009). However, it is hypothesized that physical symptoms may be more consistently detected at a later age, when an individual's cognitive reserve begins to decline (Broglio et al., 2012). The combined damage to cerebral neurons from concussive injury and aging may exacerbate the aging process, leading to clinical symptoms. Compared to age-matched controls, older adults who sustained a concussion have been found to have increased impairments in coordination, ataxia and spasticity (Rabadi & Jordan, 2001). Therefore, interventions are needed that can offset the slowing of accelerated aging in the brain following concussion.

1.1 Background TMS Measures

1.1.1 Cortical Stimulation and Corticomotor Projections

TMS is a non-invasive tool that can be used to assess or alter motor cortical physiology (Barker et al., 1985). Cortical neurons in the primary motor cortex (M1) are activated through electromagnetic induction from the TMS transducing coil, which is attached to a high voltage and high current discharge system (Barker et al., 1985, Jalinous et al., 1991). When the stimulation device is discharged, a magnetic field is produced at right angles to the coil, penetrating the scalp and skull. An electrical field is induced perpendicularly to the magnetic field. The induced currents stimulate cortical neurons producing an outward-directed trans-

membrane current in cortical axons. If depolarization of the membrane is strong enough, an action potential is triggered. These action potentials spread trans-synaptically to activate neurons that connect to cortical and subcortical areas (Groppa et al., 2012). If TMS is delivered over M1, the trans-synaptic volley activates pyramidal neurons in layer V that becomes the corticospinal tract (Gropa et al., 2012). The corticospinal tract descends through the brainstem and the spinal cord to eventually synapse on alpha motor neurons on the ventral horn of the spinal cord. Activation of the alpha motor neurons causes a muscle response that can be recorded as a motor evoked potential (MEP).

1.1.2 Motor Evoked Potential (MEP)

The MEP is a TMS parameter that reflects the excitability of the corticospinal neurons in M1. MEP's are elicited through single pulse TMS. A single pulse of TMS is delivered over the motor cortex on the contralateral side of the target muscle. The induced current alters the excitability of interneurons in M1 that indluences the net result of pyramidal neurons. The size of the MEP reflects the neuron state in M1. MEP amplitudes are affected by modulation of inhibitory and excitatory transmission in cortical networks. That is, the sum of all inhibitory and excitatory influences to the pyramidal neurons. At a consistent stimulus intensity, a higher MEP amplitude reflects a more excitable cortico-motoneuronal system. MEPs are increased by dopamine agonists and norepinephrine agonists (Klomjai et al., 2015) or depressed by agonists of fast gamma-amino-butyric acid (GABA-A) receptors. This reduction in GABA-A receptors occurs due to sodium (Na+) channel inactivation, leading to decreased action potential firing and synaptic transmission (Ziemann et al., 1996). Once an MEP is elicited, it can be recorded as an electrical signal from surface electrodes and EMG placed over the target muscle.

1.1.3 Resting Motor Threshold (RMT)

The resting motor threshold (RMT) is a TMS parameter that tests excitability of the motor cortex. It is defined as the TMS intensity that evokes an MEP of a given criterion amplitude (usually 50 uV) in a resting target muscle on 50% of trials (Rossini et al., 1994). RMT can be used to assess cortical excitability and is often used to normalize stimulation intensity across individuals. The RMT depends on the excitability of cortico-cortical axons and their excitatory contacts to corticospinal neurons, as well as through spinal mechanisms. While the RMT and MEP both reflect cortical and corticospinal excitability, they are differentially modulated by separate physiological mechanisms. The RMT reflects the influence of mainly indirect (I1) waves, which can be stimulated at lower intensities. I waves are volleys of excitatory trans-synaptic projections to the central nervous system (CNS). I1 waves reflect the earliest wave of volleys that synapse on pyramidal neurons, which occurs at a latency of approximately 1.5ms. The RMT is affected by changes in ion conductivity that influences Na+ and calcium (Ca2+) channels on cortical axons (Ziemann et al., 1998). It is also influenced by agents acting on ionotropic non-N-methyl-D-aspartate (non-NMDA) glutamate receptors that are responsible for fast excitatory synaptic transmission in the cortex (Klomjai et al., 2015). This fundamental difference in physiology allows for changes in RMT to occur without changes in MEP.

1.1.4 Cortical Silent Period (CSP)

The CSP is a single pulse TMS parameter that measures cortical inhibition. Cortical inhibition refers to suppression of neuronal firing and plays a critical role in modulating cortical output. The CSP is obtained when a suprathreshold TMS stimulus is delivered over the motor cortex, while the target muscle is tonically contracted. The “silent period” refers to the pause in

ongoing volitional electromyography (EMG) activity following the MEP elicited by the suprathreshold TMS stimulus to the motor cortical representation of the contracted muscle (Terao & Ugawa, 2002). The initial part of the CSP is due to spinal inhibitory mechanisms, such as the refractory period of pyramidal tract neurons and the H-reflex. The latter part can be explained by cortical inhibitory mechanisms. Contraction levels are kept constant during CSP assessment to ensure the spinal component constant. This allows the CSP to be an assessment of cortical inhibition. Cortical inhibition reflected by the CSP is mediated by gamma-aminobutyric acid-B (GABA-B) metabotropic receptors. A longer duration of the CSP reflects an increase in GABA-B receptor activity, compated to a lower duration of the CSP. GABA-B receptors act through a G-protein and secondary messenger pathways to activate potassium (K+) channels and block Ca2+ channels. The cell becomes more negatively charged, leading to hyperpolarization and a subsequent decrease in action potentials. Resumption of EMG activity depends on recovery of motor cortical excitability from this GABAergic inhibition that follows the TMS pulse (Chen et al., 1999). Intersession variability for CSP duration is low (<10%). Therefore, it remains a suitable measure for intracortical inhibition before and after experimental manipulation.

1.1.5 Short-Interval Intracortical Inhibition (SICI)

SICI is a paired-pulse TMS paradigm that measures ipsilateral intracortical inhibition (Berardelli et al., 2008). Paired pulse TMS, in general, involves the delivery of two consecutive TMS pulses. SICI is assessed by preceding a suprathreshold test stimulus with a subthreshold conditioning stimulus over the motor cortex. The subthreshold conditioning stimulus activates GABA-A receptor mediated intracortical inhibitory networks that influence the excitability of the corticospinal output neurons recruited by the suprathreshold test stimulus. In the case of SICI

the two stimuli are separated by an interstimulus interval (ISI) of approximately one to five milliseconds (ms) (Ziemann et al., 1996). At these intervals, the subthreshold conditioning stimulus suppresses the MEP produced by the suprathreshold test stimulus, resulting in a smaller MEP. This fast-acting synaptic inhibition is caused by the activation of GABA-A receptors, which are ligand-gated ion channels that control the flow of chloride into the cell (Ziemann et al., 1996). The increase in chloride levels, triggered by the action of inhibitory interneurons recruited by the subthreshold TMS stimulus, creates an inhibitory post-synaptic potential. The inhibitory post-synaptic potential pushes the corticospinal neurons further away from their firing threshold. The corticospinal neurons are less likely to reach their firing threshold when the excitatory effect of the suprathreshold TMS stimulus arrives, resulting in a reduction of descending corticospinal waves to the alpha motor neurons of the agonist muscle (Di Lazzario et al., 1998).

1.1.6 Long-Interval Intracortical Inhibition (LICI)

LICI is another paired-pulse TMS paradigm that measures ipsilateral intracortical inhibition of the cortex through recorded MEP inhibition. In contrast to SICI, LICI uses two suprathreshold stimuli delivered at a longer ISI of 50-200ms. Two MEP's are produced, whereby the second MEP is suppressed by the first. The first suprathreshold stimulus in LICI involves activation of slower acting inhibition, which dampens the size of the second MEP. The interstimulus interval coincides with the duration of the inhibitory post synaptic potentials that are mediated by metabotropic GABA-B receptors (McDonnell et al., 2006; Werhahn et al. 1999) These are G-protein receptors that transmit slow inhibition through the outflow of K+ from the cell, resulting in long-lasting inhibition and attenuation of the MEP. Due to differing mechanisms, there is no correlation between the degree of SICI and LICI in individuals (Sanger

et al., 2001). Unlike the CSP, LICI is likely only mediated at the cortex, rather than both the cortex and through spinal mechanisms (Fuhr et al., 1991).

1.1.7. Intracortical Facilitation (ICF)

ICF is a paired pulse TMS paradigm that measures excitability of intracortical networks in M1. A subthreshold conditioning stimulus is preceded by a suprathreshold test stimulus, with an ISI between 5-20ms. This duration activates glutamatergic mediated corticocortical neurons, thereby enhancing the MEP response (Keller, 1993). ICF may also be influenced through inhibition of GABA-A mediated neurotransmission in M1 (Ziemann et al., 1995). It is thought that ICF occurs solely due to cortical mechanisms, without altering spinal excitability (Chen et al,.1998). Therefore, ICF can provide direct insights into the excitability of the corticocortical networks in M1.

1.2 Synaptic Plasticity: Long-Term Potentiation/ Long-Term Depression

The role of the synapse is to transfer nerve impulses from one neuron to the next. Historically it was believed that synapses were relatively fixed in their strength, with limited capacity to change. However, synapses are extremely plastic and can adapt in response to various stimuli. This phenomenon is known as synaptic plasticity; one of various forms of neuroplasticity that exists in the brain. There are two forms of synaptic plasticity, long term potentiation (LTP) and long-term depression (LTD). LTP refers to the strengthening of synaptic connections, whereas LTD is associated with a decrease in lsynaptic connections. These processes are critical for learning and memory (Pascual-Leone et al., 1994).

Synaptic plasticity can occur pre-synaptically or post-synaptically. Pre-synaptic LTP begins with persistent depolarization of the pre-synaptic cell. This allows voltage-gated Ca2+ ion channels to remain open so that Ca2+ ions flow into the cell. Increased Ca2+ activates the cyclic

adenosine 3-5-monophosphate/Protein kinase (CAMP/PKA) pathway, allowing for the release of vesicles from the presynaptic terminal. These vesicles release neurotransmitters, such as glutamate, into the synaptic cleft. The permeability of Ca2+ ion channels can also be increased through retrograde neurotransmitters, such as nitric oxide.

One form of post-synaptic plasticity associated with motor learning begins when glutamate binds to the ionotropic receptors N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) on the postsynaptic cell. The opening of AMPA receptor channels allows Na+ to flow into the cell, leading to depolarization. This post-synaptic potential causes magnesium (Mg2+) to be removed from the NMDA receptor, which enables Ca2+ and additional Na+ to enter the cell. The magnitude and temporal pattern of the inflow of Ca2+ via NMDA receptors is what determines whether LTP or LTD is induced (Yang et al., 1999). A large influx of Ca2+ stimulates LTP, whereas a moderate inflow of Ca2+ allows for the LTD process to begin. During the early phase of LTP, a rapid influx of Ca2+ activates Calcium/calmodulin-dependent protein kinase II (CaMKII), triggering the phosphorylation of new AMPA receptors into the postsynaptic membrane. An increase in receptors allows for increases in glutamate binding. These processes lead to a larger post-synaptic response. Early phase LTP lasts for only a few hours. Late LTP results in more permanent changes that last between 24 hours or up to a lifetime. During late phase LTP, synaptogenesis occurs to provide permanence. A prolonged influx in Ca2+ causes AMPA receptors to be synthesized through transcription factors and gene expression. Additionally, growth factors are synthesized, which contributes to the formation of new synapses.

In contrast to LTP, LTD refers to a decrease in synaptic strength through low frequency signals or temporal unpairing of a stimulus with an action potential (Ito & Kano, 1982). Similar

to LTP, the LTD process begins with glutamate neurotransmitter acting on NMDA receptors, causing Ca2+ to flow into the post-synaptic cell. Low frequency signals causes NMDA receptors to open less frequently, leading to a moderate influx of Ca2+ in the post-synaptic membrane. This type of synaptic activity activates protein phosphatase 2B (PP2b) and inactivates CaMKII. This eventually leads to the removal of AMPA receptors from the synaptic cleft, limiting the influx of Na+. A decrease in depolarization occurs due to the post-synaptic cells ineffectivity of being excited.

1.3 Paired Associative Stimulation

Paired associative stimulation (PAS) is a paradigm that combines TMS and peripheral nerve stimulation (PNS) to induce LTP- or LTD-like effects in M1 (Stefan et al., 2000, Wolters et al., 2003). Synapses are strengthened through the near synchronous arrival of central and peripheral inputs that converge on pyramidal cells in M1. The optimal timing between PNS and TMS is critical to optimally probe LTP-like effects. An interstimulus interval of 25ms optimizes LTP-like plasticity (Stefan et al., 2000; Wolters et al., 2003), whereas an interstimulus interval of 10ms facilitates LTD-like plasticity (Wolters et al., 2003). The interstimulus interval of 10ms (PAS-10) is shorter than the time it takes for the afferent signal to reach the cortex, causing temporal unpairing and PAS-related LTD. An interval of 25ms (PAS-25) enables the afferent signal from PNS to reach the motor cortex in synchrony with the TMS pulse. PAS-25 consistently increases MEP amplitudes, indicating that PAS-25 has a general excitatory effect on the cortex (Stefan et al., 2000, Stefan et al., 2002). These excitatory effects depend on strengthening synaptic connections of the glutamatergic system, through persistent NMDA receptor activation (Stefan et al., 2002; Wolters et al., 2003). Voltage-gated ion channels, such as Na+ and Ca2+ channels also contribute to driving neuroplastic adaptations (Heidegger et al.,

2010; Hendrich et al., 2008). GABA receptor-mediated inhibition may also contribute to the LTP-like effects of PAS. Several studies have revealed a decrease in LICI following PAS-25 (Meunier et al., 2012, Russmann et al., 2009). Furthermore, an elongation of CSP duration following PAS-25 has been reported (Cirillo et al., 2009; De Beaumont et al., 2012; Stefan et al., 2000). However, SICI does not seem be affected by PAS (Stefan et al., 2002; Russmann et al., 2009). Deficits in GABA-mediated inhibition may reduce the effectiveness of PAS. For example, De Beaumont (2012) revealed a reduced efficacy to PAS in modulating MEP amplitude and CSP in individuals with a history of concussions. It is suggested that this occurs due to the enhancement of GABA-mediated inhibition that remains after sustaining a concussion. On the contrary, several mechanisms have been found to enhance the LTP response to PAS, including aerobic exercise (Singh et al., 2014). Acute aerobic exercise prior to PAS primes the brain by creating an optimal environment for LTP-like plasticity to occur. Given the sensitivity of PAS to exercise, investigating its effects in the post-concussed brain may provide valuable insights into understanding exercise and plasticity after sustaining a concussion.

1.4 Neurochemical Cascade of Concussion

The biomechanical injury of a concussion leads to a neurochemical cascade of events, including ionic shifts, neurometabolic changes and impaired neurotransmission. Shearing and stretching forces cause a disruption of the cellular membrane and opening of voltage-gated K+ channels. Efflux of K+ leads to neuronal depolarization, which promotes the release of excitatory neurotransmitters, such as glutamate. This further stimulates K+ efflux and promotes influx of Na+ and Ca2+. Energy demand increases as the Na+/K+ pump must work in overdrive to restore neuronal membrane potential. However, this increase in energy demand occurs in the setting of diminished cerebral blood flow, leading to a mismatch between energy supply and demand. A

state of hyperglycolysis prevails to overcome the cellular energy crisis. However, the influx of Ca2+ further inhibits oxidative metabolism and impairs axonal function (Choe et al., 2002). Following excitation, the brain enters a state of spreading depression in efforts to maintain homeostasis (Giza & Hovda, 2001). This short-term shift in metabolic pathways can translate into long-term, persistent adaptations and set the stage for vulnerability to repeatred injury. These shifts in metabolic adaptations are likely contributors for the neurological deficits that are experienced after sustaining a concussion (Giza & Hovda, 2001).

Long-term consequences of the neurochemical cascade following a concussion may result from alterations in brain activation. Changes in neurotransmission can lead to alterations in protein expression and synthesis (Hovda et al., 2005). For example, a decrease in sub-unit regulation of NMDA receptors occurs, which further decreases the flux of Ca2+ ions. It is thought that this occurs as a neuroprotective mechanism of Ca2+ regulation. Since glutamate-mediated NMDA receptors play a critical role in LTP/LTD-related plasticity, alterations in expression may contribute to maladaptive LTP/LTD-related plasticity. GABA receptors are also known to modulate the excitatory-inhibitory balance following a concussion. In the acute stages of concussion, GABA-mediated inhibition is decreased, whereas long-term GABA-mediated inhibition increases. It is hypothesized that this occurs as a neuroprotective mechanism to minimize further cellular injury.

1.5 Motor Cortex Plasticity Post-Concussion

One brain region that post-concussion plasticity can be assessed is at the motor cortex. TMS can be used to assess glutamatatergic and GABA-mediated neurotransmission through several single and paired pulse paradigms previously mentioned. In the sub-acute phase of concussion (<6 months post-concussion), motor cortex excitability is altered. Specifically,

reductions in ICF have been found (Power et al., 2014). It is suggested that ICF is mediated predominantly by glutamate, which is a global indicator of motor cortex excitability. Functionally, lower ICF was associated with lower maximal voluntary muscle activation and greater perceptions of force. A strong negative correlation between ICF and rate of decline of force was also observed. Studies have also reported an increased RMT (Tallus et al., 2012) and decreased MEP amplitude (Livingston et al., 2010) after sustaining a concussion. These results suggest that the motor cortex is in a state of hypo-excitability, even once clinical symptoms from the concussion reside. These alterations in synaptic transmission calls to question whether these deficits may put athletes at an increased risk of future injury. However, it is important to note several inconsistencies in the literature. Several studies have found no change in RMT compared to healthy controls (Powers et al., 2014, Livingston, 2010).

Long-term (>6 months post-concussion) cortical changes following a concussion show similar decreases in excitability. Additionally, increases in intracortical inhibition have been reported. Numerous studies have revealed that second messenger intracortical inhibition is negatively impacted through an increase in LICI and CSP duration (De Beaumont et al., 2007; De Beaumont et al., 2009; De Beaumont et al., 2012; Lewis et al., 2017; Pearce et al., 2018; Tremblay 2013). These deficits are a reflection of over-activation of neural pathways that involve GABA-B receptors, resulting in increased inhibition of the motor cortex (Ziemann et al., 1996, Tremblay et al., 2013). De Beaumont (2007) found that CSP duration was not affected by the time elapsed since their last concussion. This suggests that intracortical inhibitory networks that modulate CSP remain significantly altered regardless of the time elapsed since their last concussion. Additionally, the CSP duration further increases as number of concussions increases (De Beaumont et al., 2007). This suggests that increases in concussions further exasterbates

GABA-B receptor hyperactivity. Interestingly, SICI, which is mediated by GABA-A receptors, is not altered in those with a concussion history. Therefore, these chronic inhibitory deficits are specific to inhibitory potentials generated by slower acting 2nd messenger pathways. It is thought that an increase in GABA-B mediated inhibition only presents in the chronic phase of a concussion as during the acute phases of a concussion, GABA's role in minimal. This is because the brain is in a state of hypo-excitability, so there is no risk of glutamatergic excitotoxicity. However, once the brain returns to baseline excitability (no differences in ICF between groups), increases in LICI and CSP are documented (De Beaumont et al., 2007). Some studies also revealed longterm differences in corticomotor excitability through an increase in RMT (Lewis et al., 2017; Bernabeau et al., 2009; Tallus et al., 2011). Decreased levels of glutamine have been found in individuals after sustaining a concussion, which likely explains decreases in corticomotor excitability (Henry, 2010). On the other hand, increases in corticomotor excitability through increase in MEP amplitude's have been found in individuals with a concussion history (Meehan et al., 2017). These differences in excitability further highlight the notion that RMT and MEP amplitudes rely on different physiological mechanisms.

Long-term alterations in neurotransmission after concussions suppresses LTP/LTD-like plasticity. This deficit has been demonstrated through an impairments in plasticity-inducing protocols such as PAS (De Beaumont et al., 2012) and intermittent theta-burst stimulation (iTBS) (Meehan et al., 2017). This LTP/LTD suppression was found to be directly related to GABA-B mediated intracortical inhibitory dysfunction that persists after sustaining a concussion (De Beaumont et al., 2012). Additionally, synaptic suppression was related to impairments in implicit motor learning (De Beaumont et al., 2012). Modulation of GABA impacts LTP/LTD plasticity and motor learning through its inhibitory effects on NMDA receptors (Davies et al.,

1991). These modifications in neurotransmission and M1 plasticity calls for interventions that aim to restore glutamatergic and GABAergic neurotransmission to preconcussion levels.

1.6 Exercise and Motor Cortex Plasticity

In healthy individuals, exercise has been found to enhance M1 plasticity through alterations in neurotransmission. Cirillo & collegues (2009) found that physically active individuals are more responsive to the neuroplastic effects of PAS. This was indicated by an enhanced area under a stimulus-response curve in the physically active group, compared to sedentary individuals. These results indicate that being physically active improves responses. Several pre-post test designs were conducted to further investigate the effects of exercise on M1 excitability and intracortical inhibition. Exercise alone does not appear to modify excitability of corticospinal networks. Several studies have found no change in MEP amplitude or RMT after acute aerobic exercise (McDonnell et al., 2013; Singh et al., 2014; Smith et al., 2014; Yamazaki et al., 2019). However, exercise has been found to reduce SICI at moderate (Smith et al., 2014; Singh et al., 2014) and low-intensity (Yamazaki et al., 2019) aerobic physical activity. This suggests that acute aerobic exercise decreases GABA-A repeptor mediated inhibition in M1. Studies have also found that acute aerobic exercise increases ICF (Singh et al., 2014) and decreases LICI (Mooney et al., 2016). Collectively, increases in facilitation and decreases in intracortical inhibition may create an environment that is supportive of plasticity in M1.

The effects of exercise on processes that underlie use-dependent plasticity have been investigated. Exercise enhances LTP-like effects of PAS (Mang et al., 2014; Singh et al., 2014) and iTBS (Andrews et al., 2020) through increases in MEP amplitude (Andrews et al., 2020; Mang et al., 2014; Baltar et al., 2018; Singh et al., 2014; Andrews et al., 2020), ICF (Andrews et al., 2020) and decreases in SICI (Andrew's et al., 2020; Singh et al., 2014). Exercise may also

facilitate LTD-like plasticity. A study by McDonnell (2013) reported that low intensity aerobic exercise promoted the neuroplastic response to continuous theta burst stimulation (cTBS) through a suppression of MEP amplitudes.

It appears the timing of exercise in relation to the application of neuroplastic paradigms is vital. Studies suggest that exercise should be performed before neuroplastic paradigms, as the reverse order apparently abolishes neuroplastic adaptations. Singh (2016) reported that the neuroplastic effects of cTBS were abolished when followed by an acute bout of exercise. It was suggested that results contradicted their hypothesis of exercise enhancing the neuroplastic response because the exercise was performed after cTBS. Baltar (2018) also reported that when exercise was performed after transcranial direct current stimulation (tDCS), there were no significant changes in MEP amplitude. Thus, it was suggested that exercise should instead be implemented prior to the neuroplastic-inducing techniques. This allows exercise to be used as a 'primer' for these paradigms in order to maximize neuroplastic adaptations. These findings support the Bienenstock-Cooper-Munro theory, whereby the threshold for inducing neuroplasticity is increased following periods of postsynaptic activity (Bienenstock et al., 1982).

The overall increase in excitability and decrease inhibition after acute aerobic exercise provides favourable conditions for the induction of LTP-like plasticity (Stefan et al., 2002). LTP-like plasticity that is achieved by changes in M1 excitability is a key mechanism underlying early mechanisms that lead to sustained changes in ability, known as motor learning (Rioult-Pedotti, 2000). While motor learning involves the activation of several functional networks in various brain regions, LTP-like plasticity in M1 is integral for motor learning. Acute exercise has been shown to improve motor skill acquisition (Snow et al., 2015) and retention (Roig et al., 2012). Additionally, Mang et al., (2014) found that a single bout of high-intensity interval training

(HIIT) primed LTP-like neuroplasticity and promoted sequence-specific motor learning, as indicated by a reduced time lag in continuous tracking motor learning task. This is achieved by repeated stimulation of the corticomotor pathways, which alters synaptic structure and function, and eventually cortical reorganization (Rioult-Pedotti, 2000).

1.7 Mechanisms Behind Exercise and Motor Cortex Plasticity

It is thought that aerobic exercise creates an optimal environment in M1 for the early induction of plasticity. Potential mechanisms include altered cerebral metabolism, cortisol levels and the upregulation of neurotransmitter activity and brain derived neurotrophic factor (BDNF). Aerobic exercise is associated with approximately a 20% global increase in cerebral blood flow (CBF) (Smith et al., 2014). Blood supplies essential neuronal energy substrates such as glucose and lactate, which is involved with cortical excitability. CBF through the middle cerebral artery (the main artery supplying blood to M1) exhibits an inverted-U relationship with exercise intensity, with its peak at around 60% VO2 max (Moraine et al., 1993). As exercise intensity increases, brain glucose uptake decreases (Gonzalez-Alonso et al., 2004; Kemppainen et al., 2005). In contrast, increased exercise intensity is associated with an increase in cerebral uptake of lactate (Ide et al., 2000), demonstrating a shift in cerebral fuel usage. High lactate levels from exercise or when administered intravenously are associated with an increase in M1 excitability and decreased RMT (Coco et al., 2010). This is because lactate promotes N-methyl-D-aspartate (NDMA) receptor activity and the subsequent intracellular cascades that result in the increased expression of plasticity related genes (Yang et al., 2014). Lactate also increases BDNF levels, suggesting another link between lactate production and plasticity.

Additionally, neurochemical modulations from exercise may explain cortical excitability changes. This may occur through alteration in neurotransmitter levels such as dopamine,

serotonin and norepinephrine. Dopamine is a catecholamine neurotransmitter that is synthesized in the brain from its precursor levodopa (L-DOPA). In M1, dopamine works on the inhibitory GABAergic interneurons by activating or inhibiting D1 and D2 receptors, respectively. The effects of dopamine in M1 are difficult to measure. It can either promote or inhibit motor activity, depending on the receptors activated. Dopamine concentration is the determining factor of its postsynaptic effects (Luft & Schwarz, 2009). During exercise, global dopamine levels are consistently shown to increase (Foley & Fleshner, 2008), however local changes in M1 have not been investigated. At rest, the firing of M1 neurons and subsequent movement generation are significantly impaired by dopamine receptor blockade (Par-Brownlie & Hyland, 2005). A study by Ziemann et al. (1997) revealed that dopaminergic agonists and antagonists strongly influences both intracortical inhibition and facilitation. Collectively, it appears that dopamine enhances plasticity through the modulation of intracortical excitability.

Serotonin is a monoamine neurotransmitter that is synthesized in the brain. Their receptors are G-protein coupled receptors, which allows serotonin to play a key role in the modulation of postsynaptic neurons via the activation of signalling pathways (Struder & Weicker, 2001). Serotonin appears to have a general excitatory effect on network activity, as it promotes depolarization of neural networks (Struder & Weicker, 2001). The effect of exercise on serotonin levels is somewhat unclear as previous studies have seen serotonin levels to increase (Chauloff et al., 1997), decrease (Lukaszyk et al., 1983) or remain unchanged after aerobic exercise (Dey et al., 1992). It is likely that serotonin mediates nonspecific effects of exercise on M1, as their activity remains elevated during the execution of a motor behaviour (Jacobs & Fornal, 1999).

Norepinephrine is a catecholamine neurotransmitter that is synthesized from dopamine. Acute aerobic exercise is associated with an increase in circulating norepinephrine levels and increased norepinephrine turnover in the cortex, both during and after exercise (Gerin & Pivat, 1998; Pagliari & Peyrin, 1995). Norepinephrine appears to have an excitatory effect on the motor cortex, as norepinephrine reuptake inhibitors enhances M1 excitability and ICF (Herwig et al., 2002, Plewnia et al., 2002). Additionally, norepinephrine agonists increase MEP amplitudes and ICF (Ziemann et al., 1996). This may have implications on motor learning, as pharmacological blockade of norepinephrine receptors suppresses the induction of LTP-like plasticity (Korchounov & Ziemann, 2011).

The steroid hormone cortisol may play a part in the plasticity of the motor cortex following exercise. This hormone is released during the final step of the central stress response system, known as the hypothalamic pituitary adrenal (HPA) axis. The HPA axis is stimulated during exercise, thereby increasing circulating cortisol levels. A strong positive linear relationship between exercise intensity and cortisol levels exists (Girard & Garland, 2002). Low and moderate intensity exercise is associated in decreases in cortisol, whereas intense exercise increases cortisol levels (McDonnel et al., 2013, Morris et al., 2009). High levels of cortisol hinders LTP like plasticity (Sale et al., 2008), whereas low levels of cortisol facilitates the induction of LTP like plasticity (McDonnel et al., 2013). The mechanisms behind this relationship are not fully understood, however the literature suggests that this transition in LTP-like plasticity function is due to modulations in receptor activity. At low blood cortisol levels, cortisol binds to mineralocorticoid. As cortisol concentrations increases, receptor saturation occurs and cortisol instead binds to glucocorticoid (Pittenger & Duman, 2008).

BDNF is a protein that is involved with promoting neuroplasticity through supporting the growth of new synapses. BDNF plays a critical role in both early and late LTP. BDNF increases neuronal firing rates via the TrKB receptor. This receptor activates a range of second messenger pathways that can phosphorylate NMDA receptors, thereby enhancing excitatory post-synaptic potentials. BDNF also mediates intracortical inhibition. This is achieved by reducing the amount of GABA-A receptors, leading to a reduction in the amplitude of postsynaptic inhibitory currents (Brunig et al., 2001). Acute exercise increases circulating BDNF (Ferris et al., 2007). Additionally, BDNF levels are positively correlated with exercise intensity (Winter et al., 2007). However, a study my McDonnel et al (2013) revealed that there was no correlation between BDNF and enhancement of postexercise neuroplasticity in the motor cortex. Therefore, more research is needed to directly evaluate the effects of BDNF on M1 plasticity measures.

1.8 Dose-Response Recommendation for Exercise

Despite a wide variety of evidence regarding exercise and neuroplasticity, the optimal intensity and duration of exercise that induces maximal neuroplastic effects is not well known. It is of clinical importance to determine this relationship in order to prescribe an exercise plan that will maximally enhance motor learning and neuroplasticity. Studies regarding exercise and motor cortex plasticity have used either treadmill running or a stationary bike as their mode of exercise. Results show motor cortex excitability increases in both treadmill running (Thacker et al., 2019) and cycling interventions (Andrews et al., 2020; Mang et al., 2014; McDonnell et al., 2013; Singh et al., 2014).

It has also been suggested that the intensity and duration of exercise, rather than exercise mode, is a stronger predictor of neuroplastic benefits. The combined research suggests that shorter bouts of HIIT or longer bouts of low to moderate intensity aerobic exercise may be more

beneficial in promoting neuroplastic benefits compared to prolonged aerobic exercise at a high intensity. In an animal study by Thacker et al. (2019), moderate exercise showed increased indicators of motor cortex plasticity compared to maximal intensity exercise in rats. Furthermore, McDonnell et al. (2013) found that prolonged low intensity exercise induced motor cortex excitability changes, but not for moderate to high intensity exercise. This was supported by Smith et al. (2018) who recorded no facilitation in MEP responses in prolonged high intensity exercise (80% predicted heart rate reserve (HRR)). Andrews et al. (2020) found that HIIT showed greater neuroplasticity compared to prolonged moderate intensity exercise. It is suggested that the negligence of prolonged high intensity exercise in facilitating neuroplastic response is due to an associated increase in cortisol levels. This elevation in cortisol can effectively inhibit neuroplasticity induction (Sale et al., 2008). Additionally, brain glycogen levels are reduced following long bouts of moderate to high intensity exercise (Matsui et al., 2012). A systematic review by Mellow et al. (2020) speculates that lower intensity continuous exercise and HIIT may allow cortisol and glycogen levels to be maintained at levels that does not hinder neuroplastic responses of the motor cortex.

2.0 Aims and Hypotheses

Aim 1: To determine the effects of an acute bout of aerobic exercise on the potential for use-dependent plasticity in motor cortex (reflected by excitability of the corticospinal networks) in those with a history of concussion.

Hypothesis 1A: Acute aerobic exercise will enhance the ability of the plasticity inducing protocol, PAS, to increase corticomotor excitability at a suprathreshold TMS intensity, compared to sedentary activity paired with PAS. This will be demonstrated by an increase in the MEP amplitude after acute aerobic exercise, compared to after sedentary activity.

Hypothesis 1B: Acute aerobic exercise will not change corticomotor excitability, as indicated by the minimal intensity to evoke an MEP, compared to sedentary activity when paired with PAS. This will be demonstrated by no change in RMT after acute aerobic exercise, compared to sedentary activity.

Aim 2: To determine the effects of an acute bout of aerobic exercise on the potential for use-dependent plasticity in motor cortex intracortical networks that modulate corticospinal output.

Hypothesis 2A: Acute aerobic exercise will enhance the ability of the plasticity inducing protocol, PAS, to decrease intracortical inhibition compared to sedentary activity paired with PAS. This will be demonstrated by a decrease in SICI after acute aerobic exercise, compared to after sedentary activity.

Hypothesis 2B: Acute aerobic exercise will enhance the ability of the plasticity inducing protocol, PAS, to decrease intracortical inhibition compared to sedentary activity paired with PAS. This will be demonstrated by a decrease in LICI after acute aerobic exercise.

Hypothesis 2C: Acute aerobic exercise will enhance the ability of the plasticity inducing protocol, PAS, to decrease intracortical inhibition compared to sedentary activity paired with PAS. This will be demonstrated by a decrease in the CSP after acute aerobic exercise.

Hypothesis 2D: Acute aerobic exercise will enhance the ability of the plasticity inducing protocol, PAS, to increase intracortical excitatory networks compared to sedentary activity paired with PAS. This will be demonstrated by an increase in ICF after acute aerobic exercise.

3.0 Methods

3.1 Participants

Sixteen individuals between the ages of 18-35, with a history of at least one clinically diagnosed concussion were recruited for the study. Of the sixteen participants, eleven were female and five were male. The age range of participants was 19-33 years, with an average age of 23 +/- 3.32 years (+/- standard deviation). Participants were recruited via flyers posted around the Waterloo community, or through recruitment emails sent to the University of Waterloo students. Participants were required to be asymptomatic and sustained their last concussion at least 6 months prior to testing. The time elapsed since the most recent concussion was at least 6 months prior to participation in the study. Their first concussion must have occurred after the age of twelve. The average time elapsed since their last concussion was 3.7 +/- 2.62 years. The number of concussions sustained ranged from one to five concussions. The average number of concussions was 2 +/- 1.34. Concussion history was recorded through the Michigan TBI Identification method. Baseline remaining concussion symptoms were assessed through the post-concussion symptom scoring (PCSS) inventory to ensure participants were asymptomatic (Lovell & Collins, 1998). The measure consists of 22 questions that relate to post-concussive symptoms. Participants rate each symptom according to a scale ranging from 0-6. The greatest possible score is 132 and the lowest possible score is 0. The average score on the PCSS was 4.44 +/-3.69. Further exclusion criteria were also applied: Medications that affect the central nervous system, a history of seizures, or a history of any neurological diseases/injury (other than concussion). All participants achieved a moderate or vigorous level of physical activity, as determined by the International Physical Activity Questionnaire (IPAQ). Completion of the Get Active Questionnaire (GAQ) was required to ensure that

individuals could safely participate in exercise. Six participants were categorized as being moderately active by the IPAQ. This includes three or more days of vigorous exercise at 20 minutes or more/day or five or more days of moderate intensity exercise and/or walking at minimum 30 minutes/day or five or more days of a combination of the activities mentioned above achieving a minimum of 600 MET-minutes/week. The remaining ten participants were categorized as being highly physically active. This classification equates to vigorous-intensity exercise on at least three days/week or seven or more days consecutively of walking or moderate to vigorous intensity exercise at a minimum of 3000 MET minutes/week. The average MET-minutes per week was 4375.94 +/-3320.88. Finally, participants received financial compensation of 10 dollars per hour for participating in the study.

3.2 Design

The study was a cross-over design; participants served as the intervention and the control. The order of the exercise and control sessions was randomized across participants. Upon entry to the lab, participants underwent baseline screening to ensure the inclusion criteria was met. Exercise and TMS screening questionnaires were completed to ensure participants could safely participate in exercise and TMS studies. Once written informed consent was acquired, baseline TMS measures were conducted. These included the RMT, MEP amplitude, ICF, CSP, LICI and SICI. The order of assessments was randomized across participants. Twenty pulses were delivered for each TMS measure (MEP, CSP, ICF, SICI, LICI). Measures were randomized across participants, but the order remained consistent within the session (Pre, Post1, Post2) and across sessions (Intervention, Control). Next, individuals completed the intervention or control task. For the control task, participants watched a 25-minute documentary. The exercise intervention involved biking at a moderate intensity for 20 minutes.

After heart rate measures resumed to resting point, all participants received PAS. Post-test TMS measures occured at two timepoints: 1) 5 minutes following PAS and 2) 30 minutes following PAS. Participants returned to the lab to complete the second session (intervention or control). Each session was collected at least 48 hours apart.

3.3 TMS measures and set-up protocol

After pre-screening and written consent was obtained, participants were placed in a chair to undergo baseline TMS measures. Surface electrodes (Ag-AgCl) were placed on the right first dorsal interosseous (FDI) and right abductor pollicis brevis (APB) muscle bellies and their reference points, to record its EMG activity. TMS was performed using a Magstim BiStim^2 stimulator and figure 70 mm diameter figure-8 coil (Magstim, Whitland, UK). The coil was positioned on the left motor cortex, at an angle of 45 degrees to the mid-sagittal line. The BrainSight^{TM} neuronavigation system (Rogue Research, Montreal QC) was used to help guide the placement of the coil to the motor region of the right FDI muscle, by using a template MRI. This ensured that the coil was at an optimal position for eliciting MEPs in the target muscle. MEP's were recorded using LabChart 8 software in conjunction with a Quad BioAmp and PowerLab 4/26 acquisition system (AD instruments, Colorado Springs, Colorado, USA). Data was amplified (x1000), digitized (x40000 Hz) and filtered (bandpass filtered 3-1000 Hz, notch filter-60 Hz). The RMT was determined through the TMS Motor Threshold Assessment Tool (MTAT). The RMT intensity was determined as the stimulus intensity that corresponded to the 50% chance of evoking an peak-to-peak MEP amplitude of at least 50uVin the resting FDI muscle. Using the MTAT, the stimulus intensity needed to evoke an MEP with a 1mV peak-to-peak amplitude was also detemined. The 1mV threshold intensity was applied to assess MEP amplitude.

Paired pulse measures were assessed using the following parameters for the conditioning stimulus (CS), test stimulus (TS) and inter-stimulus interval (ISI): a) SICI (CS=80% and TS = 120% of RMT, 2.5 ms ISI); b) LICI (CS = 120% and TS = 120% of RMT, 100 ms ISI); and c) ICF (CS = 80% and TS = 120% of RMT, 12 ms ISI). SICI and ICF were intermixed with reference single pulses (SP) of 120% RMT in the following order of trials (10 SICI, 10 SP, 20 ICF, 10 SP, 10 SICI). LICI was conducted separately from this sequence. SICI was quantified by the ratio of condioned/unconditioned MEP amplitude. A larger percent value indicated less SICI (less inhibition). ICF was also quantified by the conditioned/unconditioned MEP amplitude. A larger value was indicative of increases in ICF (more facilitation). LICI was quantified by the percentage of the conditioned/unconditioned MEP. The unconditioned MEP was the MEP induced by the first suprathreshold stimulus, whereas the conditioned MEP was the MEP induced by the second suprathreshold stimulus.

CSP duration was assessed through single pulse TMS. Subjects performed an isometric voluntary contraction of their FDI muscle at 10% of their maximal contraction while 20 pulses at 150% RMT were delivered. Participants were given in-time visual feedback of EMG activity to ensure the intensity of muscle contraction remains consistent. The CSP duration was measured manually by the period of the onset of EMG suppression that follows the MEP, until EMG activity resumes. These TMS paradigms were repeated at the two following timepoints: 5- minutes post PAS and 30 minutes post PAS.

3.4 Intervention vs Control Session

The exercise session consisted of a 20-minute continuous moderate intensity biking session on a stationary bike. Prior to exercise a baseline resting heart rate (HR) measure was collected. Participants biked at 60% of their heart rate reserve ((220 – age(years) – resting

HR)*0.6)+resting HR)). Heart rate was continuously monitored by a FT1 Polar watch and T31 polar chest strap. Intensity was subjectively measured through the modified Borg Rating of Perceived Exertion (RPE) scale. Participants began with a five-minute warm-up. The first two minutes consisted of biking at 70 revolutions per minute (RPM) to become familiarized with the bike. The remaining three minutes of the warm-up aimed to increase intensity to reach the calculated target heart rate. Next, participants biked continuously for 20 minutes at a moderate intensity. Pedalling rate was maintained between 60-80 RPM. Participants performed a 3-minute active cooldown on the bike between 60-70 RPM. Following completion, participants rested and HR was monitored until resting HR was achieved.

The control session involved watching a 25-minute episode of the Netflix docuseries "72 Cutest Animals" (Mitchell, 2016). The video was selected to ensure attention and arousal was maintained during the rest period of the session. The video was also aimed to be minimally mentally taxing, as mental fatigue can interfere with neuromuscular function (Morris & Christie, 2020).

3.5 Paired Associative Stimulation (PAS)

All participants received PAS. PAS was used to probe M1 excitability changes that was induced by acute aerobic exercise. The paradigm consisted of a slow-rate repetitive low-frequency electrical stimulation of a median nerve, combined with TMS over the FDI representation of M1. The median nerve was stimulated at 0.1Hz, followed by a 25ms pause before the delivery of TMS. Electrical stimulation was delivered using a DS7A constant high voltage stimulator (Digitimer, North America LLC, Fort Lauderdale, Florida, USA). Stimulus intensity was determined by determining the intensity needed to evoke a twitch of 0.2mV.

TMS was applied at an intensity to evoke an MEP of 1mV. In total, 100 pairs of stimuli will be delivered, with a 10 second interpulse interval.

3.6 Statistical Analysis

Statistical analyses were conducted using the R environment for statistical computing (R Development Core Team, 2019) and the following packages: "rstatix", "tidyverse", “emmeans”, “sjstats”, “lmertest”, "lme4". Separate Session (Sedentary, Exercise) x Time (Pre, Post-5 minutes, Post-30 minutes) repeated measures ANOVAs were conducted to assess the effect of exercise on MEP amplitude, RMT, ICF, LICI and SICI. A linear mixed model was conducted to assess the effect of exercise on CSP duration to account for missing data points. Significant Session x Time interactions were decomposed by assessing the simple main effect of Session for each dependent variable. Greenhouse-Geisser epsilon corrections and Bonferroni corrections for multiple comparisons were employed where appropriate.

4.0 Results

4.1 Participant Characteristics

Table 1 shows means and standard deviations for general participant characteristics and concussion and physical activity history. Table 2 shows means and standard deviations for the aerobic exercise data.

4.2 Exercise Data

Resting heart rate (HR) for participants ranged between 57-72 beats per minute (BPM). The average resting HR of all participants was 64.56 +/- 4.70 BPM. The average target HR was 144.1 +/- 3.00 BPM. BORG RPE scores ranged from 4-6. The average BORG RPE was 5.44 +/- 0.89. During the exercise session, participants stayed within 10% of their target HR of 60% HRR. One participant biked at 55% of their HRR, as subjective intensity ratings on the BORG scale began to exceed a score of 6.

Table 1- General participant characteristics and concussion and physical activity history

n	16
Age	22.9 +/-3.3
Sex	11F, 5M
Number of Concussions	2.3 +/-1.3
Time Elapsed Since Last Concussion (Years)	3.7
MET's	4375.9 +/-3320.9

Table 2- Aerobic exercise data

Average HR	64.6 +/-4.7
Target HR	144.1 +/-3
RPE	5.4 +/-0.9

4.3 TMS Analysis

4.3.1 MEP amplitude. The two-way repeated measures ANOVA on MEP amplitude revealed a significant main effect of Time ($F_{2,30}$=5.48, GGe=0.80, p=0.016, n_p^2=0.27). Neither the main effect of Session ($F_{1,15}$=0.55, p=0.47, n_p^2=0.04) or the Session x Time interaction were significant ($F_{2,30}$=0.34, GGe=0.91, p=0.70, n_p^2=0.02). Post-hoc comparisons for the main effect of time demonstrated a significant increase in MEP amplitude from Pre to Post1 (p=0.014) but not Pre to Post2 (p=0.095) or Post1 to Post2 (p=1.00) (Figure 1).

The two-way repeated measures ANOVA on absolute MEP amplitude values revealed a significant main effect of Time ($F_{2,30}$=12.05, GGe=0.96, p=0.000064, n_p^2=0.48). Neither the main effect of Session ($F_{1,15}$=2.24, p=0.16, n_p^2=0.13) or the Session x Time interaction were significant ($F_{2,30}$=1.55, GGe=0.89, p=0.23, n_p^2=0.094). Post-hoc comparisons for the main effect of time demonstrated a significant increase in absolute MEP amplitude from Pre to Post1 (p=3.96 x 10^{-5}) and pre to post 2 (1.00 x 10^{-3}) but not post 1 to post 2 (p=0.1) (Figure 3).

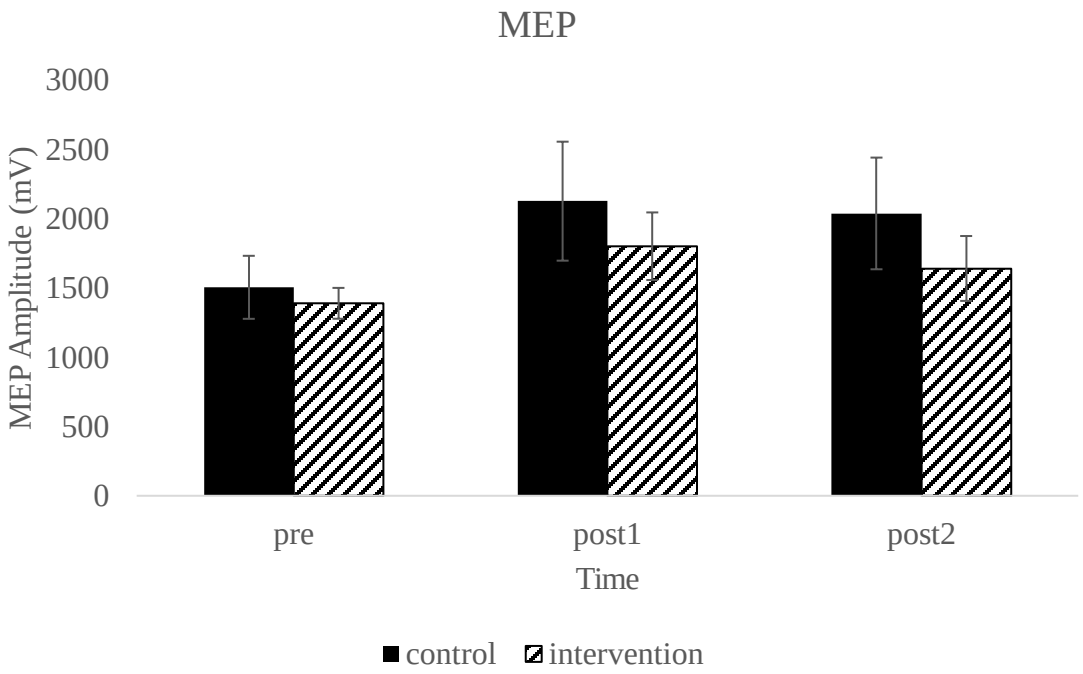
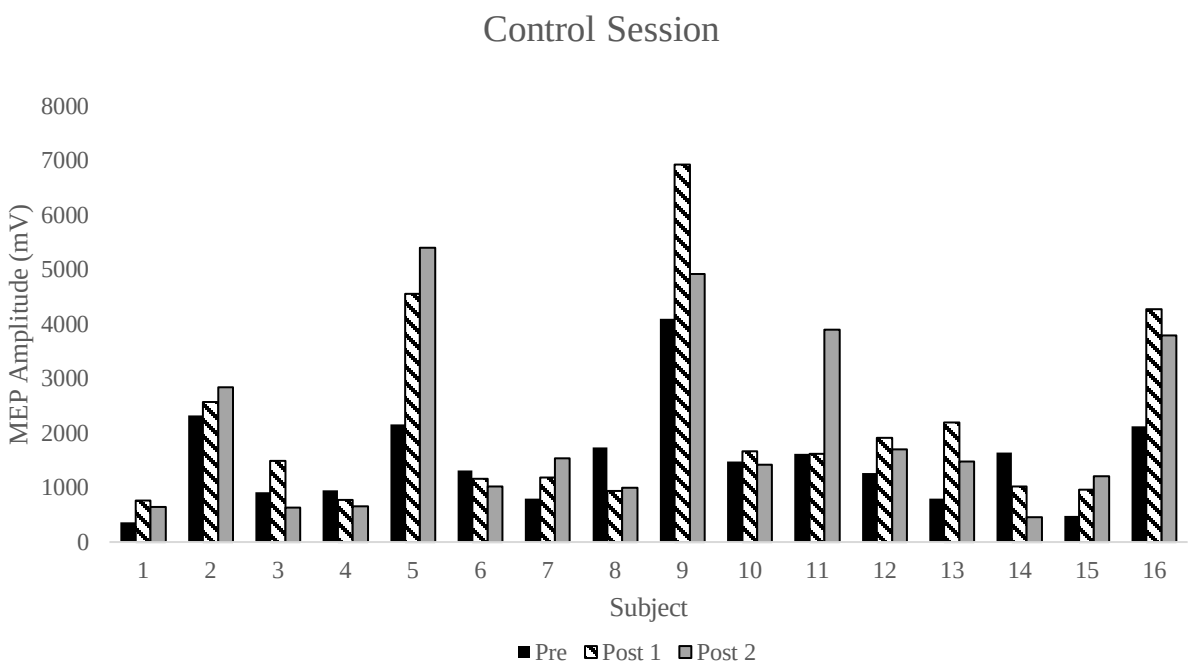


Figure 1 - Average MEP amplitude for each time point in the control and intervention session

A.



B.

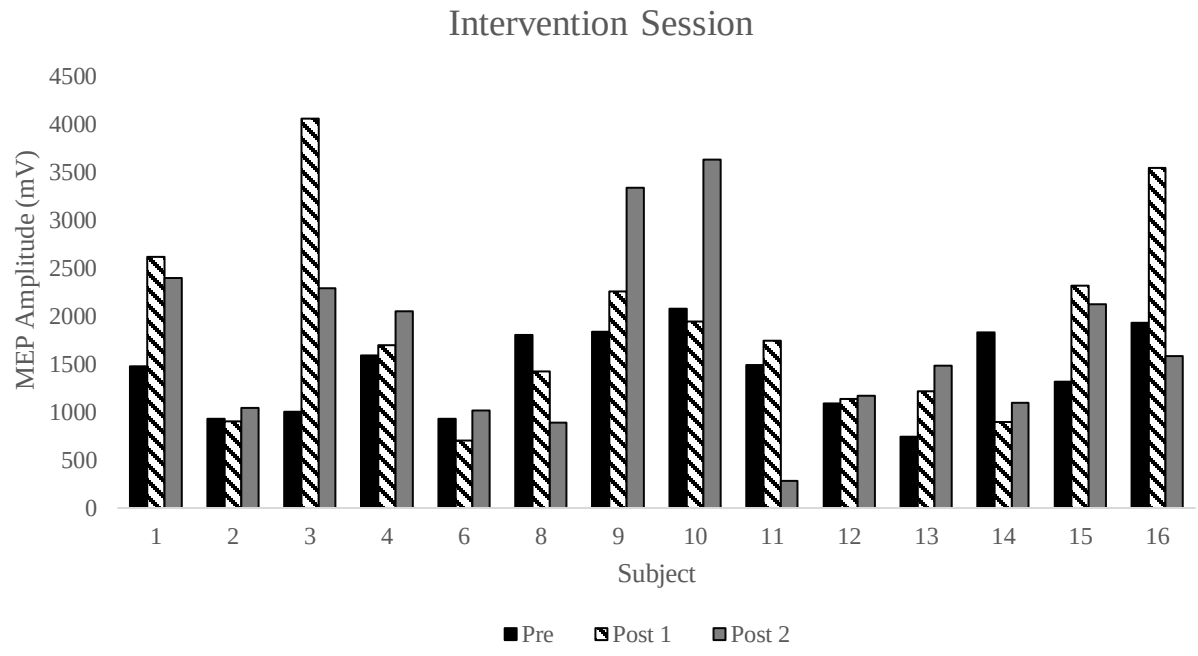


Figure 2– Individual MEP amplitude data for Control (A) ans Intervention (B)l session

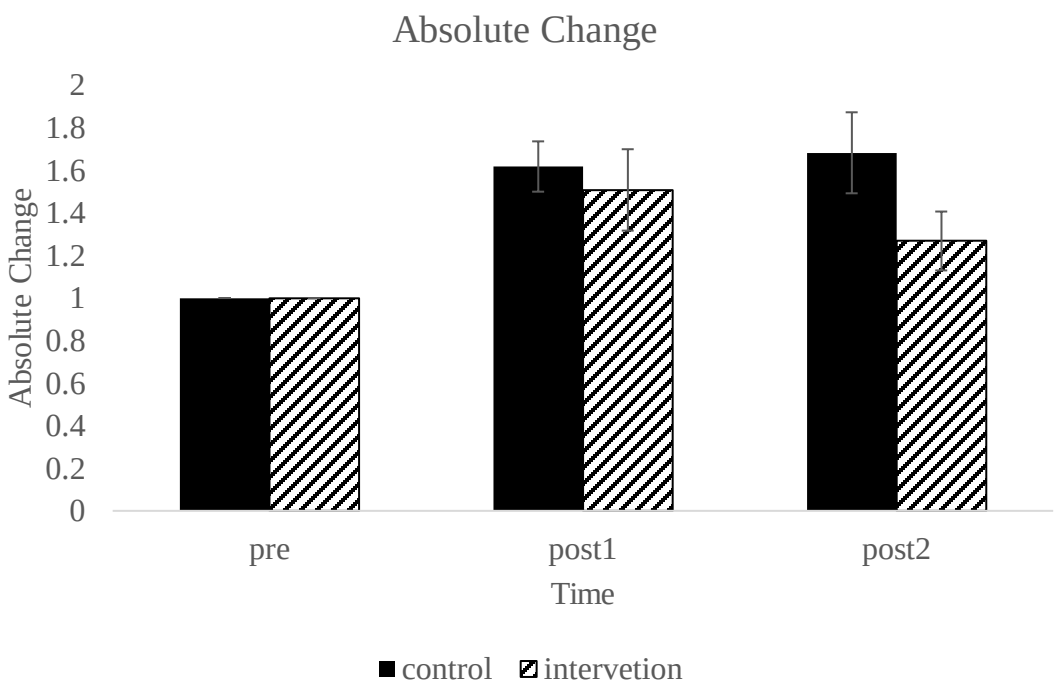


Figure 3- Absolute change in MEP amplitude values for each time point in the intervention and control session

4.3.2. RMT. The two-way repeated measures ANOVA on RMT revealed a non-significant main effect of Time ($F_{2,30}$=0.36, GGe=0.90, p=0.70, $n_p^2 = 0.01$) and Session ($F_{1,15}$=1.00, p=0.33, n_p^2=0.062). The Session x Time interaction was not significant ($F_{2,30}$=0.80, GGe=0.77, n_p^2=0.051) (Figure 4).

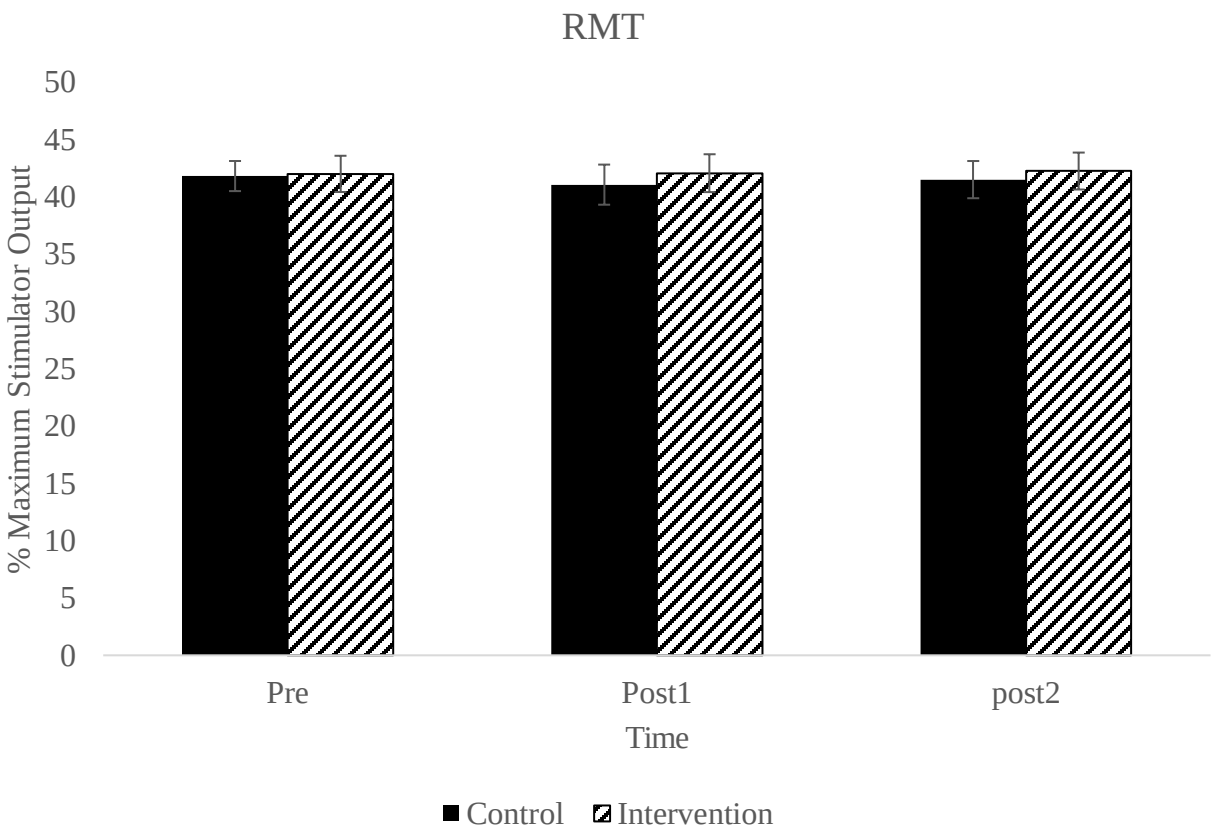
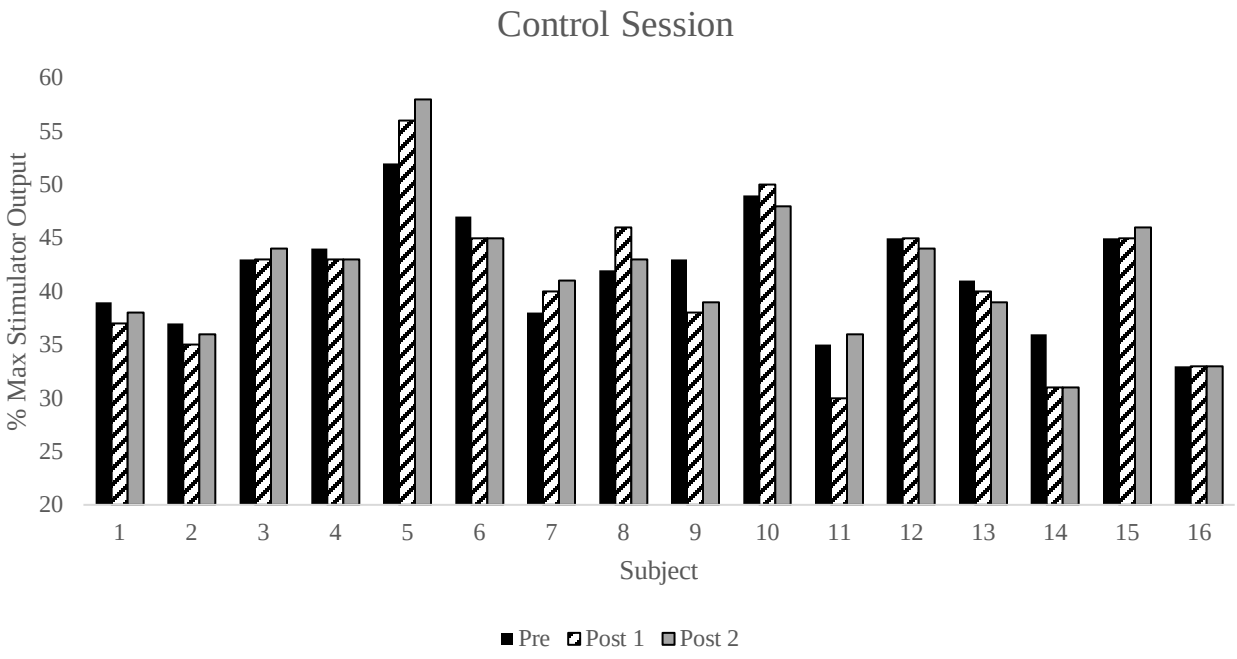


Figure 4- Average RMT for each time point in the Intervention and Control session.

A.



B.

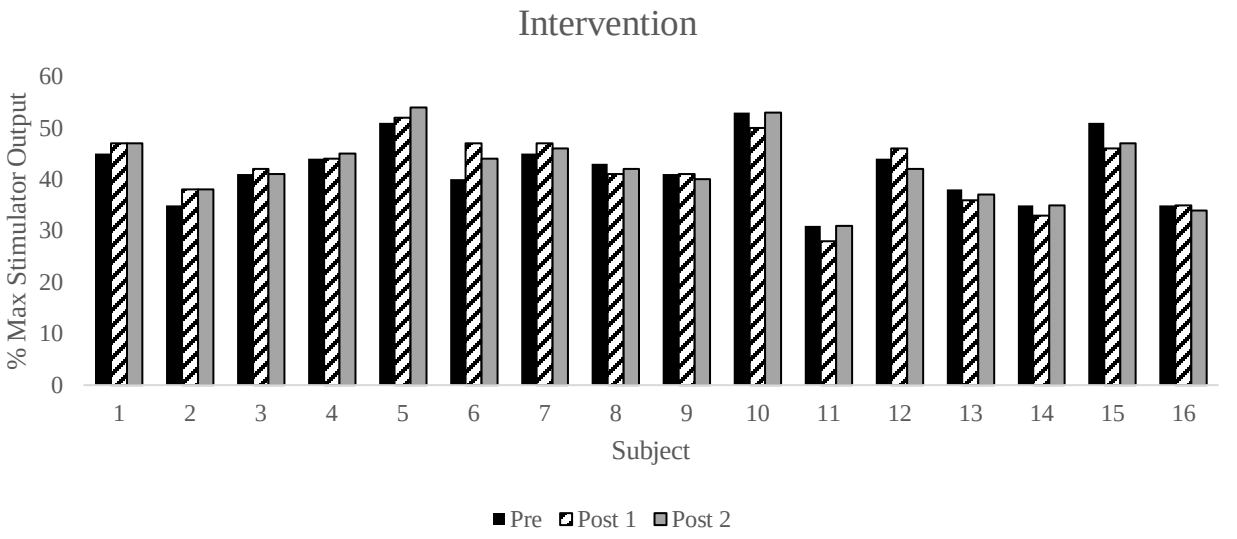


Figure 5 – Individual RMT data for Control (A) and Intervention (B) session

4.3.3. SICI. The two-way repeated measures ANOVA on SICI revealed a significant Session x Time interaction ($F_{2,30}$=4.55, GGe=0.74, p=0.032, n_p^2=0.25). Neither the main effect of Time ($F_{2,30}$=2.04, GGe=0.95, p=0.15, n_p^2=0.13) or Session ($F_{1,15}$=0.39, p=0.54, n_p^2=0.027). Post-hoc comparisons for the interaction revealed a significant decrease in SICI from Pre to Post1 for the intervention session (p=0.0039) (Figure 7).

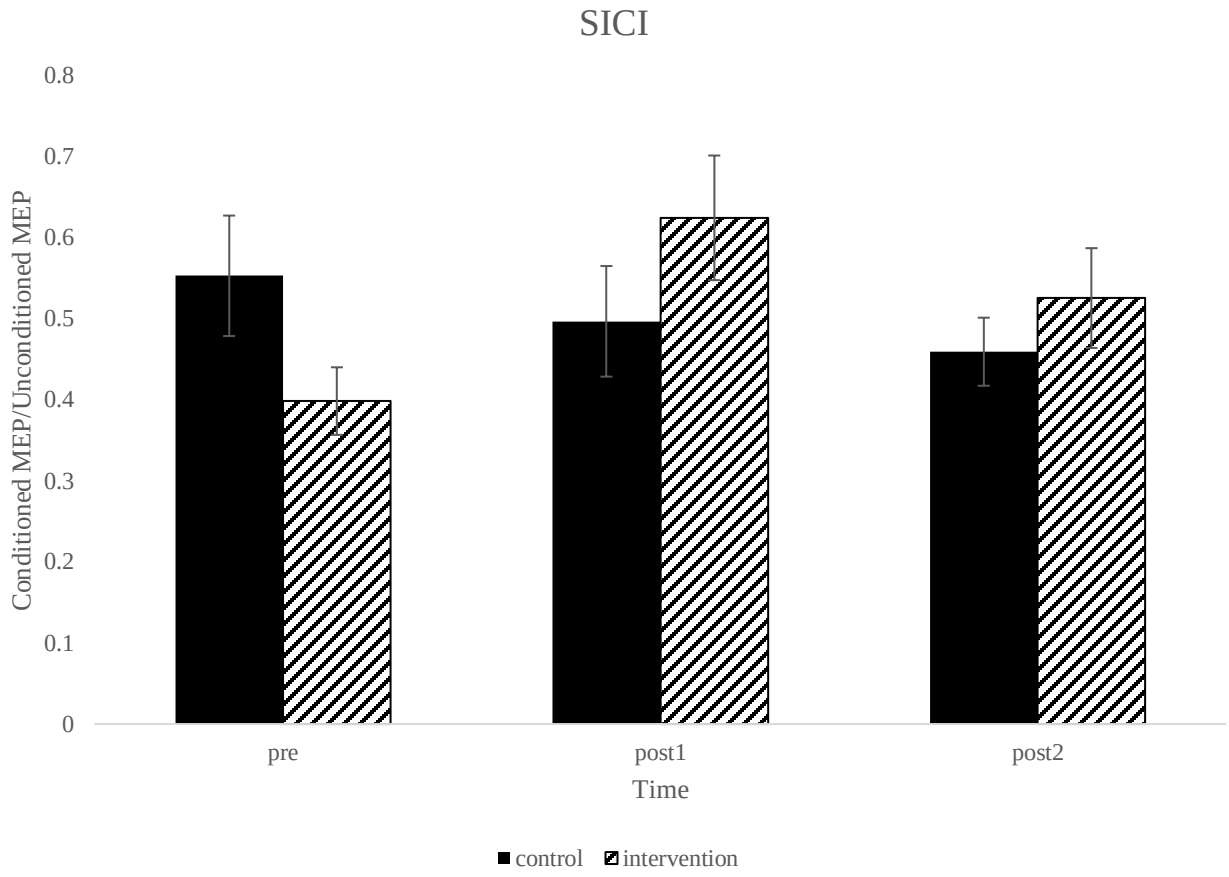
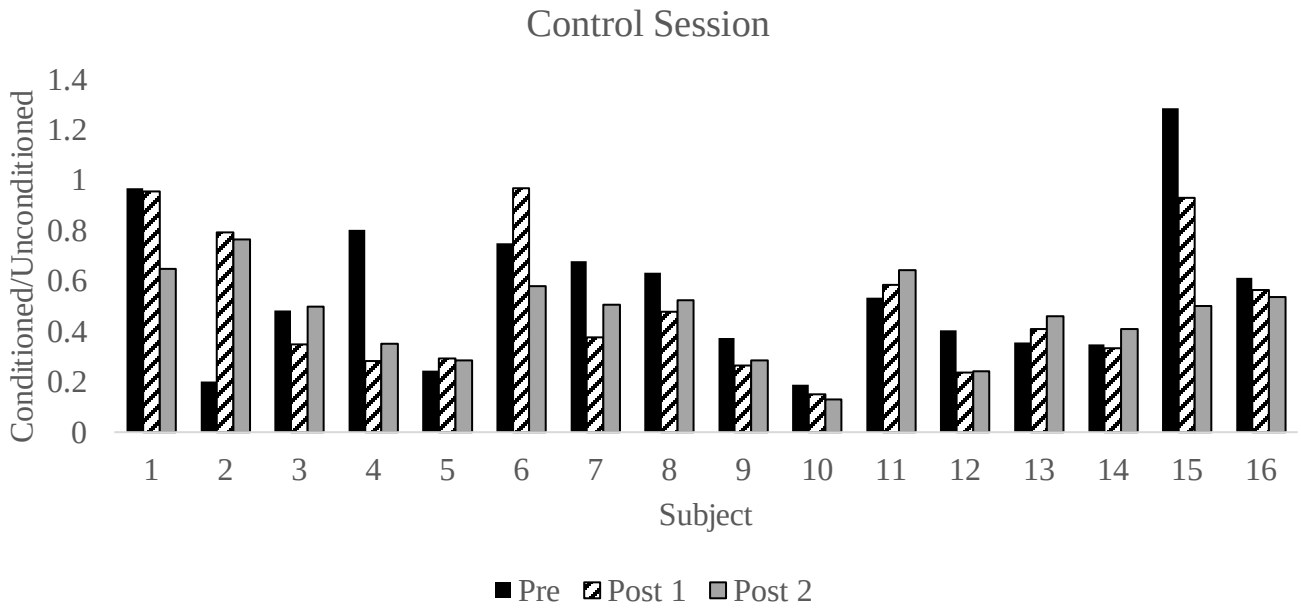


Figure 6– Average SICI for each time point in the Intervention and Control session

A.



B.

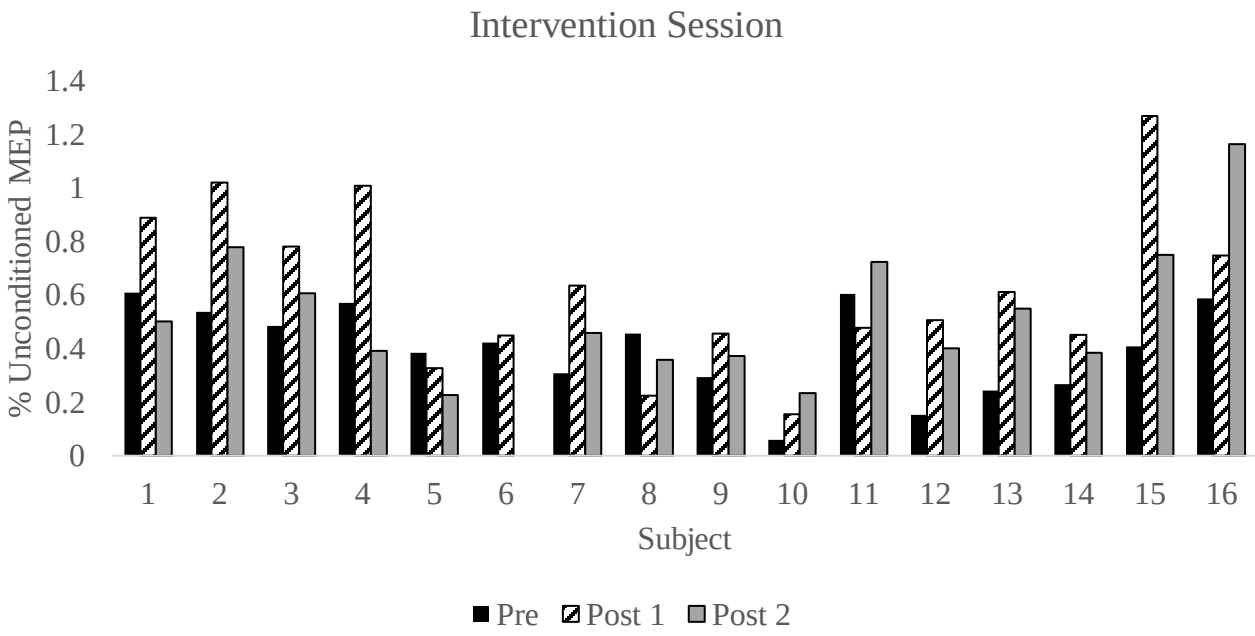


Figure 7– Individual SICI data for Control (A) and Intervention (B) session

4.3.4. ICF. The two-way repeated measures ANOVA revealed no significant main effect of Time ($F_{2,30}$0.12, GGe=0.78, p=0.84, n_p^2=0.009) or Session ($F_{1,15}$=0.17, p=0.69, n_p^2=0.012). The Session x Time interaction was not significant ($F_{2,30}$=1.07, GGe=0.98, p=0.36, n^2=0.071) (Figure 8).

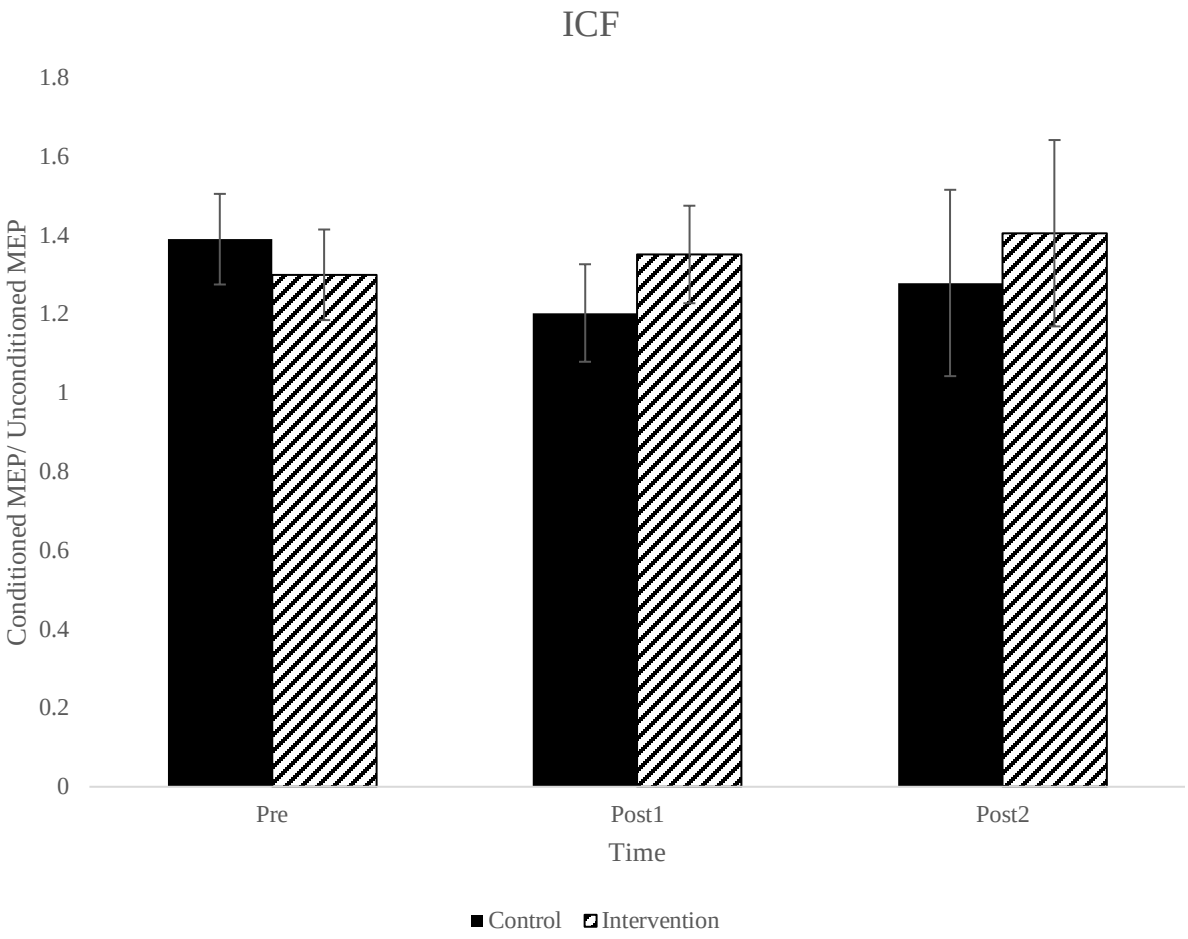
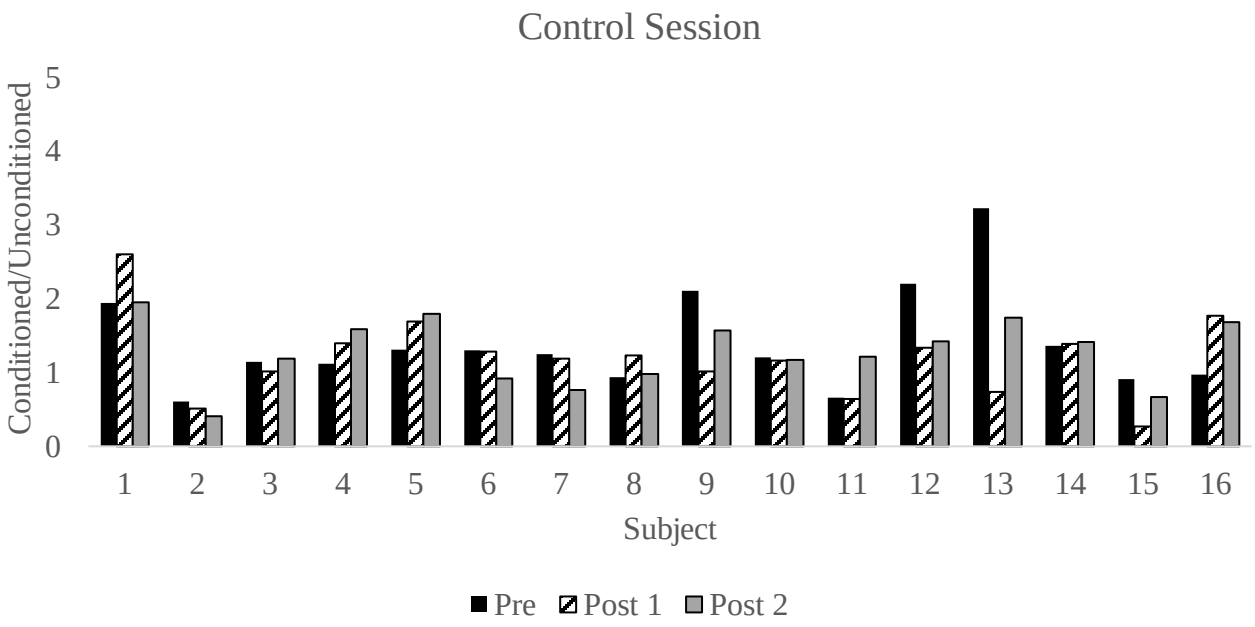


Figure 8– Average ICF for each time point in the intervention and control session

A.



B.

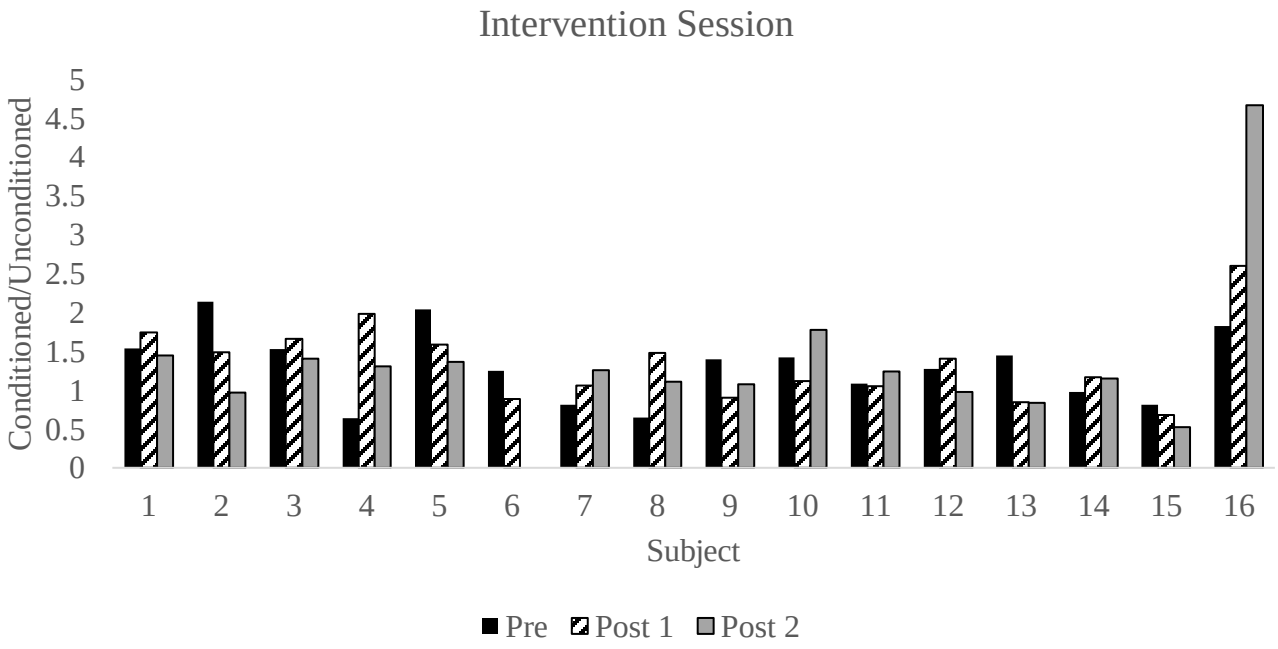


Figure 9- Individual ICF data for Control (A) and Intervention (B) session

4.3.5. LICI. The two-way repeated measures ANOVA revealed no significant main effect of Time ($F_{2,30}$=0.97, GGe=0.97, p=0.39, n_p^2=0.065) or Session ($F_{1,15}$=0.002, p=0.96, n_p^2=0.00016). The Session x Time interaction was not significant ($F_{2,30}$=0.68, GGe=0.69, p=0.46, n_p^2=0.046) (Figure 10).

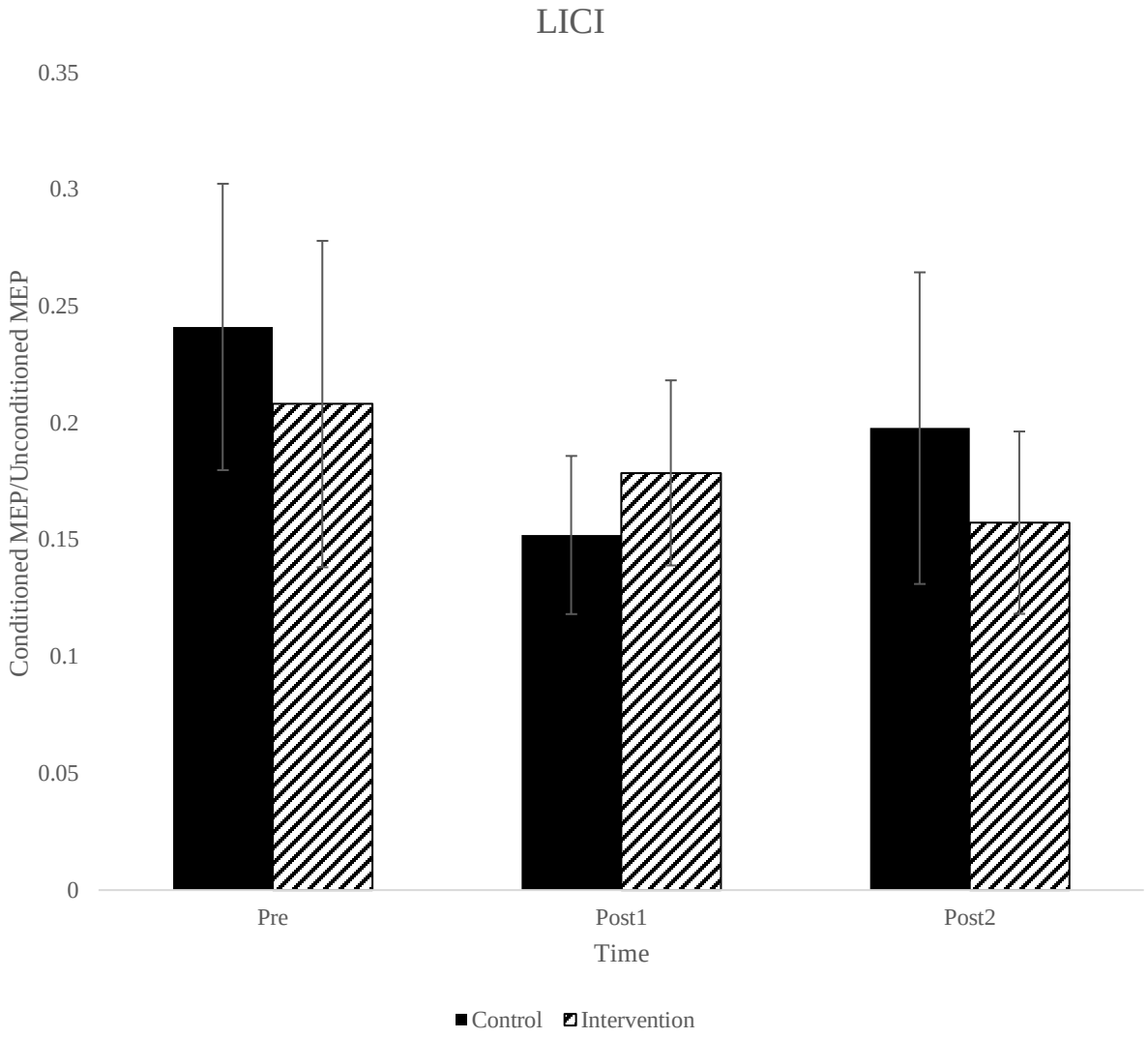
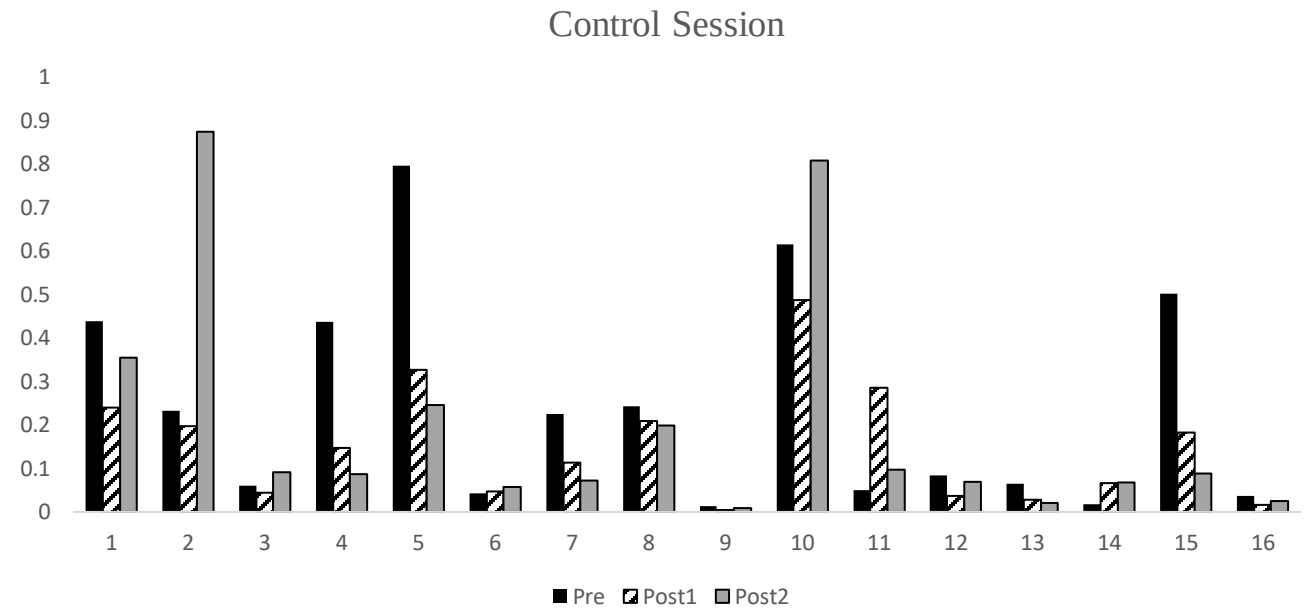


Figure 10– Average LICI for each time point in the intervention and control session

A.



B.

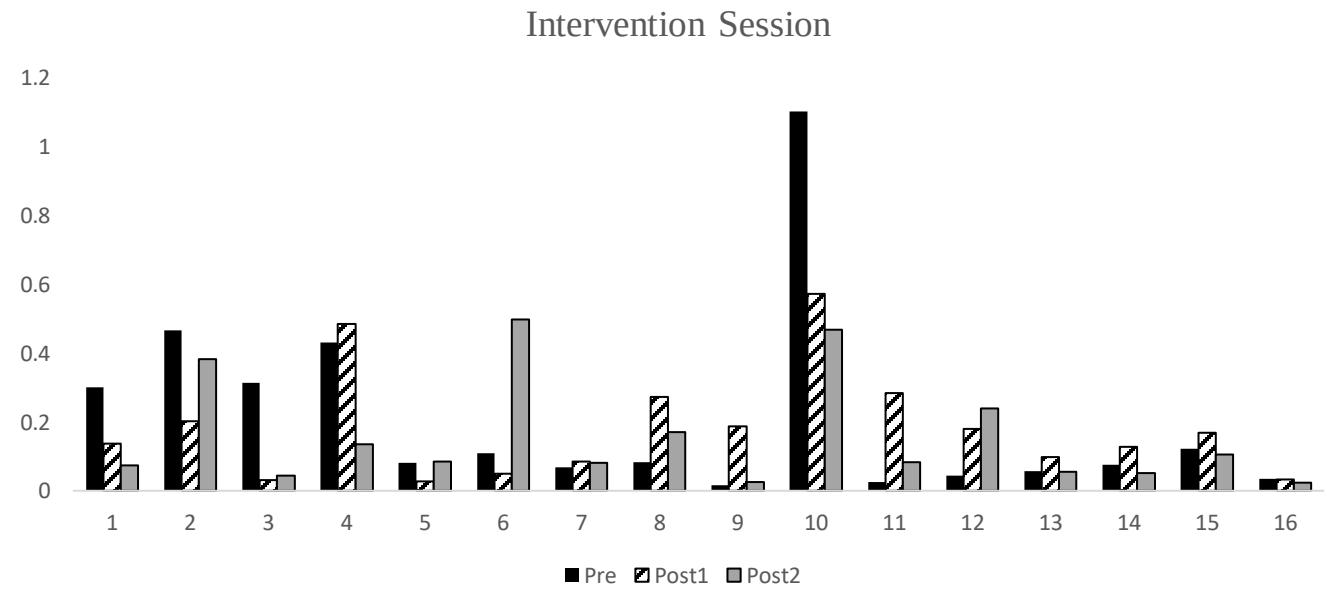


Figure 11- Individual LICI data for Control (A) and Intervention (B) session

4.3.6. CSP. The linear mixed model revealed no significant main effect of Time ($F_{2,30}$=1.84, p=0.17, n_p^2=0.05), or Session ($F_{1,15}$=2.17, p=0.15, n_p^2=0.03). The Session x Time interaction was not significant ($F_{2,30}$=1.19, p=0.31, n_p^2=0.0.03) (Figure 12).

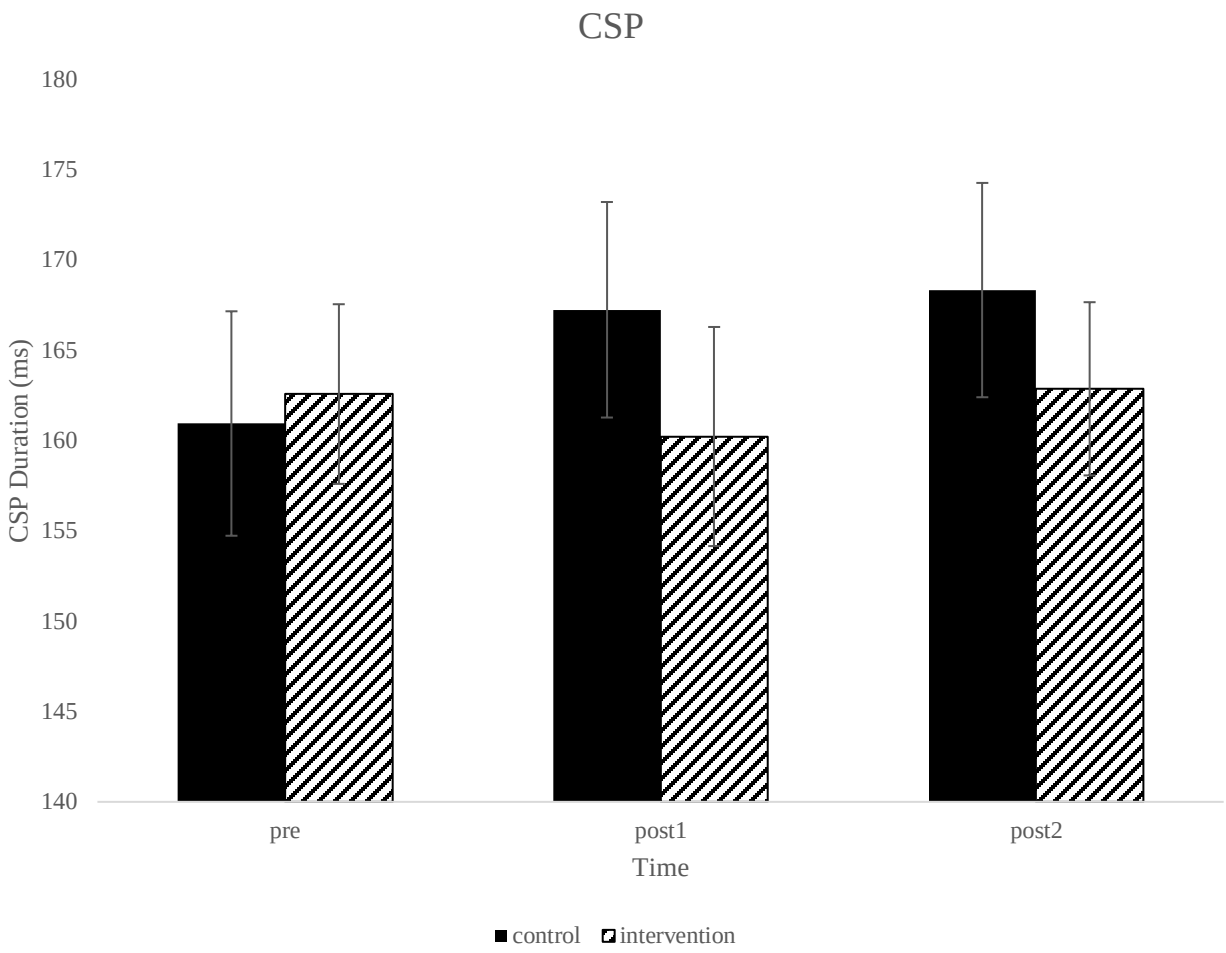
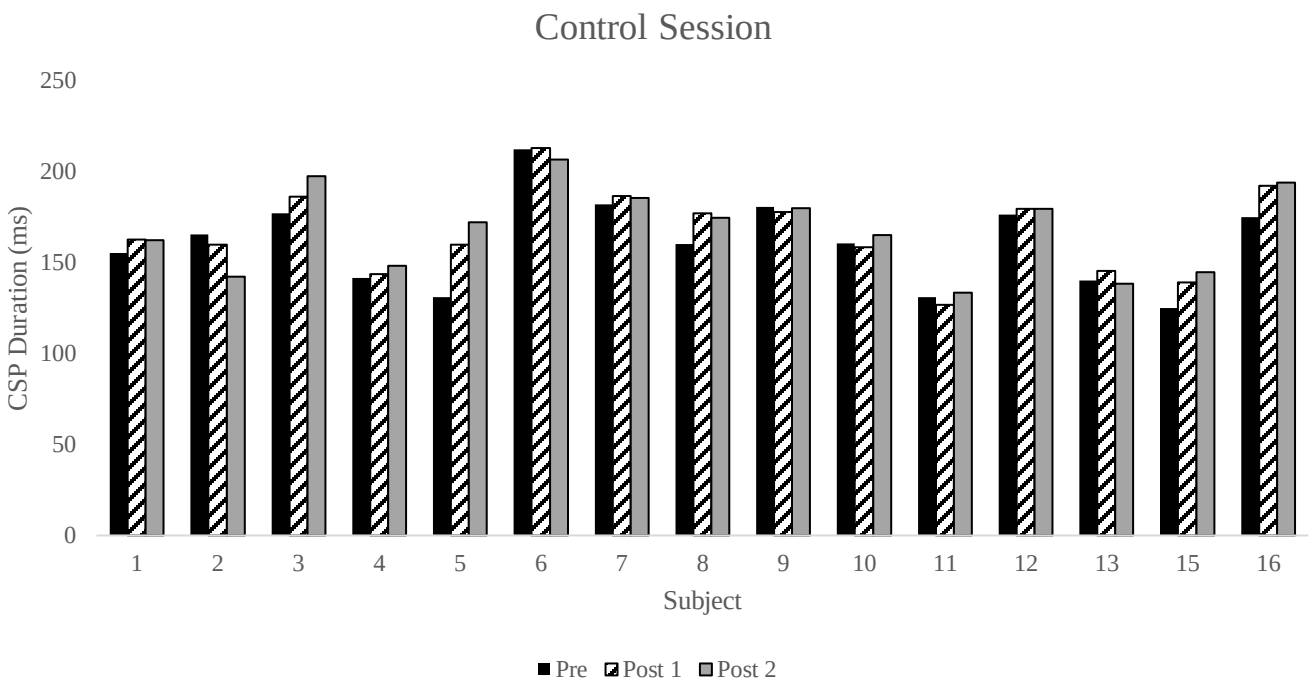


Figure 12– Average CSP for each time point in the Intervention and Control session

A.



B.

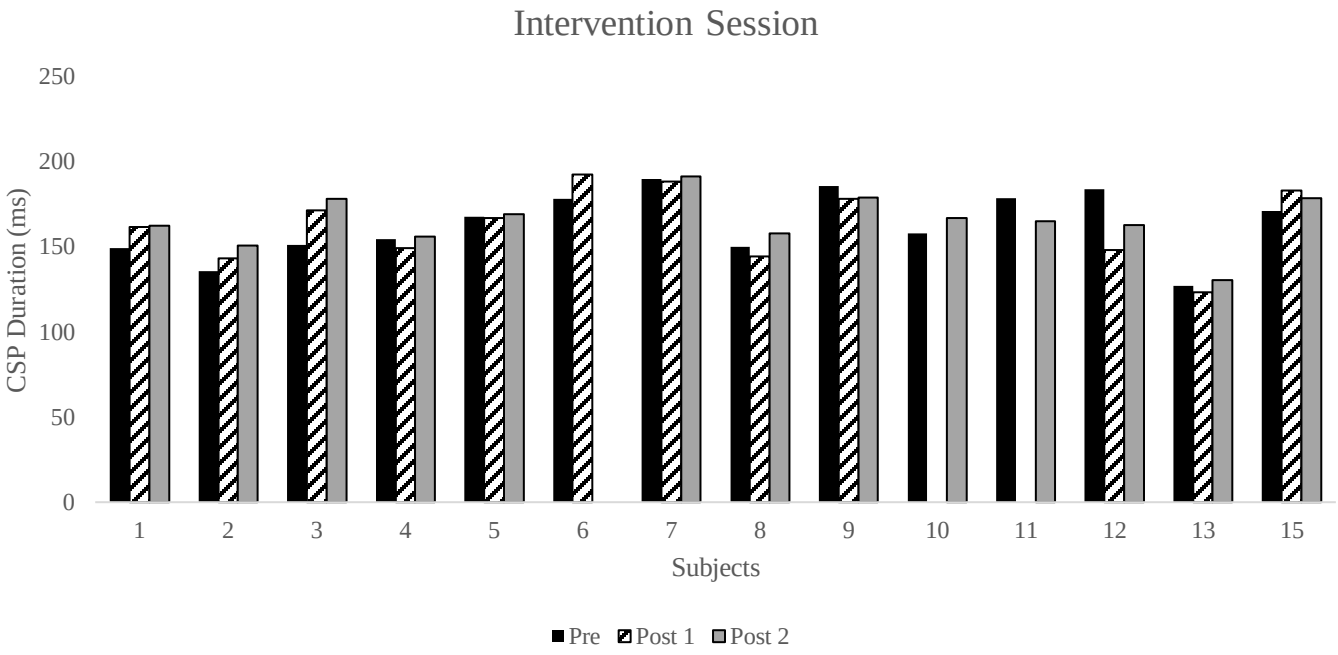


Figure 13 - Individual CSP data for Control (A) and Intervention (B) session

5.0 Discussion

This study investigated the effects of acute aerobic exercise on motor cortex plasticity in those with a concussion history. The main finding of this study was that acute aerobic exercise modified GABA-A intracortical activity that facilitates PAS-induced plasticity in individuals with a history of concussions. Specifically, SICI decreased immediately after exercise+PAS, compared to PAS alone. However, acute aerobic exercise did not enhance PAS-related plasticty through further increases in MEP amplitude.

The first objective of this study was to investigate the effects of acute aerobic exercise on the potential for use-dependent plasticity in M1, through examining excitability of the corticospinal networks. It was hypothesized that excitability would increase through an increase in MEP amplitude after exercise precedes PAS (intervention session), compared to PAS alone (control session). However, our study showed a similar increase in MEP amplitude in the intervention and control session. This suggests that excitability was increased in the target muscle after PAS, regardless of whether exercise preceded PAS or PAS alone. The similarity across sessions is in contrast to what Singh (2014) reported in non-injured controls. The discrepancy may be due to differences in how cortical excitability was measured. While this study assessed cortical excitability through MEP amplitude at a 1mV threshold, Singh (2014) used recruitment curves. It is possible that assessing cortical excitability through MEP amplitude at only one intensity failed to capture differences in excitability at higher intensities.

Although the goal of PAS-25 in this study was to induce LTP-like plasticity, great interindividual variability in PAS responses has been found (Fratello et al., 2006; Müller-Dahlhaus et al., 2008). Factors such as age, sex and baseline cortical excitability play a role in the magnitude or direction of excitability response to PAS. It is suggested that only around 75%

of healthy young adults show an LTP-like increase in MEP amplitude after PAS (Stefan et al., 2004). The remaining are considered PAS "non-responders," through a decrease or unchanged MEP amplitude after undergoing PAS. Decreases in MEP amplitude following PAS is an indication of another form of synaptic plasticity: LTD. In our study, four out of sixteen participants displayed evidence of LTD-like plasticity after undergoing PAS. This is comparable to control populations mentioned above. Given the great interindividual variability in PAS responses, merely considering LTP-like responses from PAS may limit the complete understanding of PAS and exercise on M1 plasticity. To account for the inter-individual variability in the response to PAS, plasticity was assessed as absolute values. This allows for assessment of the magnitude of plasticity, regardless of whether LTP or LTD-like plasticity was induced. While our results did not show any significant interaction between time and the session completed, moderate effect sizes were found. Interestingly, the magnitude of plasticity was higher in the PAS alone session, compared to the PAS+exercise session for the Post-2 measure. This finding suggests that moderate intensity aerobic exercise may create an unfavourable environment to enhance PAS-related plasticity in individuals with a concussion history.

A possible explanation for this finding could be due to the longterm alterations in glutamate and GABA-mediated neurotransmission that is found in individuals with a concussion history. It is thought this occurs as a neuroprotective mechanism to prevent glutamatergic excitotoxicity that occurs in the acute phases of a concussion. Increases in GABA-mediated inhibition and decreases in glutamate mediated neurotransmission is associated with compromised LTP/LTD-like plasticity (De Beaumont et al., 2012). Specifically, elevations of GABA-B mediated intracortical inhibition contributes to the suppression of LTP/LTD-like plasticty through the blocking of glutamatergic NMDA receptors (Davies et al., 1991). In healthy individuals, acute

aerobic exercise enhances M1 plasticity by creating an optimal environment for the induction of LTP-like plasticity (Singh et al., 2014). It is possible that the longterm concussion induced alterations in synaptic plasticity creates an unfavourable environment and restricts the potential for exercise to enhance LTP-like plasticity.

Decreases in M1 plasticity after acute aerobic exercise may partially be explained by exercise-induced changes in the steroid hormone cortisol. A positive linear relationship exists between exercise intensity and cortisol levels. High circulating cortisol is associated with an impairment of plasticity, potentially via suppression of NMDA receptor activity (Sale et al., 2008; McDonnel et al., 2013). It is possible that aerobic exercise was performed at an intensity high enough to suppress NMDA receptor activity and impair plasticity. Although cortisol levels at a moderate intensity of aerobic exercise facilitates M1 plasticity in healthy individuals (McMorris et al., 2009), the threshold in which cortisol levels change from beneficial to detrimental may be lower in the post-concussed brain.

Alternatively, our results could be explained by fatigue induced in the FDI muscle. Although cycling only requires the use of lower limb musculature, slight contraction of hand musculature is required to grasp the handles on the bike. Fatiguing voluntary contractions in the target muscle evokes changes in MEP's (Taylor & Gandevia, 2001). While this explanation cannot be ruled out, fatigue is unlikely to be a major contributing factor of a lack of exercise induced enhancement of M1 plasticity. Firstly, participants were instructed to rest their hands on the handles without gripping firmly in order to minimize fatigue in the hand muscles. Additionally, there was no change in RMT after cycling. Since RMT is also impacted by central fatigue, there would likely be a change in RMT if fatigue was induced in the FDI muscle.

Consistent to our hypothesis, acute aerobic exercise had no effect on the RMT. This is consistent with past literature that does not show a change in RMT after aerobic exercise (Singh et al., 2014, Yamazaki et al., 2019). No change was expected, as GABA, dopamine, norepinephrine, serotonin and acetylcholine has no effect on the RMT. Additionally, this study revealed that PAS had no effect on RMT, which is consistent with past literature (Stefan et al., 2000; Sale et al., 2007;Russmann et al.,2009). Therefore, these results suggest that RMT is not affected by acute aerobic exercise in individuals with a concussion history.

The second objective of this study was to investigate the effects of acute aerobic exercise on the potential for use-dependent plasticity in M1, by examining intracortical networks that modulate corticospinal output. It was hypothesized that exercise would decrease intracortical inhibition through a decrease in GABA-A and GABA-B receptor related inhibition. Consistent with our hypothesis, there was a significant decrease in GABA-A mediated inhibition immediately after undergoing exercise + PAS, compared to PAS alone. Decreases in GABA-A mediated inhibition was found immediately following PAS. This finding is consistent with past work by Singh (2014), that found a decrease in SICI after exercise+ PAS, compared to PAS alone in healthy individuals. However, Singh (2014) also found decreases in SICI 30 minutes post PAS, whereas this study did not reveal significant decreases at this time point. While the interaction was not significant at this time point, figure 7 reveals that SICI appears to continue to decrease. It is possible that the results are underpowered to detect a significant difference in SICI 30 minutes post-PAS. The notion that acute exercise decreases SICI is consistent with past work for many exercise intensities, including low-intensity aerobic exercise (Yamazaki et al., 2019), moderate intensity (Smith et al., 2014;Singh et al., 2014, Lulic et al., 2017) and high-intensity exercise (George et al., 2019).

Plasticity in M1 is dependent upon its net-state of inhibitory and excitatory activity (Sanes et al., 2000). GABA is the primary inhibitory neurotransmitter in the brain, and is released from inhibitory synapses to modulate the excitability of pyramidal cells. In this study, GABA-A receptor-mediated inhibition is decreased following acute aerobic exercise and PAS in individuals with a concussion history. This reduction in intracortical inhibition is critical for M1 plasticity and motor learning (Ziemann et al., 1996). As such, exercise can create favourable conditions for the induction of M1 plasticity. It is important to recognize that reductions in GABA-mediated inhibition occurred without a change in MEP amplitude. This suggests that exercise does not directly affect excitability of the pyramidal cells, but rather modulates the intracortical networks to these cells. Modulation of the MEP amplitude is dependent upon many facors, including the summation of all inhibitory and excitatory inputs. This suggests that there is no direct correlational relationship between SICI and MEP amplitude.

The mechanisms whereby aerobic exercise decreases intracortical inhibition are not completely understood. However, a few theories have been proposed. Firstly, exercise increases the secretion of BDNF. This neurotrophic factor promotes the growth, survival and plasticity of neurons. In rat models, BDNF suppresses intacortical inhibition by reducing GABA-A receptor activity (Brunig et al., 2001). Thus, it is possible that BDNF exerts the same effect in the M1 of human subjects. Another possible mechanism of exercise-induced decreases in GABA-A mediated inhibition is through an increase in the neurotransmitter dopamine. Another potential mechanism behind exercise-induced decreases in intracortical inhibition is from an increase in dopamine. Dopamine has been found to influence intracortical inhibition through its effects on GABAergic interneurons (Ziemann et al., 1997). Global dopamine levels are increased during aerobic exercise, however its direct effects on M1 have not been investigated. While it is

speculated that exercise increases dopamine levels in M1, further research is needed to confirm this hypothesis.

ICF measures activity of the excitatory glutamatergic interneuron activity in M1. It was hypothesized that ICF would be higher after the exercise session, compared to the control session. Contrary to the hypothesis, no significant differences in ICF were found between sessions. However, small effect sizes were found that should be addressed. Small decreases in ICF were found in the control session after undergoing PAS for both timepoints (5-minutes post-PAS and 30-minutes post-PAS). In contrast, small increases in ICF were found in the intervention session after undergoing exercise and PAS in both post-intervention timepoints. These results may indicate that exercise increases glutamatergic interneuron activity to facilitate an excitatory response in M1. However, small effect sizes should be interpreted with caution. When looking at the individual data, increases in ICF were not consistent across participants. This leads us to believe that meaningful exercise-induced increases in ICF in the population studied is unlikely.

Past work that assessed exercise and ICF in healthy individuals should be taken into consideration when interpreting our results. Singh (2014a) found that ICF increased after acute bout of aerobic exercise. However, a later study by Singh (2014b) found no increases in ICF and PAS, compared to PAS alone. They proposed that these discrepancies could be due to PAS inducing a suppression of ICF in order to maintain excitability levels within a physiological range. This hypothesis could particularly hold true for individuals with a concussion history. Given that individuals with a history of concussions have longterm alterations in glutamatergic neurotransmission, a lack of exercise-induced increases in ICF could be explained by a neuroprotective mechanism to prevent further increases in glutamatergic excitotoxicity.

Additionally, the discrepancy in studies could be due to timing. Changes in ICF have been found immediately after exercise, which is not possible when exercise precedes PAS. Further research including an exercise session without PAS would be valuable to gain a full understanding of the effects of exercise on ICF in this population.

Individuals with a concussion history present with longterm increases in GABA-B receptor-mediated inhibition. One way that this has been detected is through an increase in LICI (Pearce et al., 2014; Lewis et al., 2017). The effects of acute aerobic exercise on LICI are not consistent. Some studies have demonstrated no change in LICI (Singh et al., 2014; Yamazaki et al., 2019), while Mooney (2016) found a decrease in LICI after aerobic exercise. Despite these inconsistencies in healthy individuals, it was hypothesized that exercise would decrease GABA-B mediated intracortical inhibition in M1 through a decrease in LICI, in individuals with a concussion history. This was hypothesized as post-concussion related increases in GABA-B receptor-mediated inhibition may create a larger window for exercise to exert its excitatory effects on M1. However, results demonstrated that exercise combined with PAS and PAS alone had no effect on LICI. Therefore, this study suggests that acute aerobic exercise has no effect on GABA-B mediated inhibition in individuals with a concussion history. Consistent with healthy individuals, exercise favourably exerts its excitatory effects on GABA-A mediated inhibition, over GABA-B mediated inhibition. This is not surprising as there is little correlation between SICI and LICI (McDonnell et al., 2006; Sanger et al., 2001). The SICI subthreshold conditioning stimulus activates ionotropic GABA-A receptor intracortical inhibitory neurons. On the other hand, the suprathreshold stimulus in LICI activates a different pool of neurons associated with metabotropic GABA-B receptor intracortical inhibitory neurons.

The CSP is another assessment of intracortical inhibitory network activity in M1. The CSP is mainly a reflection of GABA-B receptor-mediated activity (Chen et al., 1999;McDonnell et al., 2006), and may be partially mediated by GABA-A receptor activity (Inghilleri et al., 1996). CSP duration is prolonged in individuals with a history of concussions. Past research on CSP duration, PAS and exercise is limited. A study by Mooney (2016) revealed that light intensity aerobic exercise has no effect on CSP duration. Given that CSP duration is prolonged in individuals with a history of concussions, it was hypothesized that exercise would enhance the excitability effects of PAS by decreasing GABA-B mediated inhibition. This would be indicated through a decrease in CSP duration. However, results revealed no change in CSP duration from PAS and exercise or from PAS alone. This suggests that exercise and PAS has no effect on the intracortical inhibitory networks that are associated with CSP duration in individuals with a concussion history. These results are not surprising, as there is currently no evidence to suggest that exercise can alter CSP duration.

6.0 Limitations

The current study has several limitations that should be considered. Firstly, this study did not include an exercise-alone session. Each participant underwent either PAS and exercise or PAS alone. The goal of PAS in this study was to induce LTP-like plasticity. Exercise was used as a means to create an optimal environment that facilitates the induction of LTP. However, the effects on PAS and many of the TMS measures assessed are variable. The only TMS measure that is consistently affected by PAS is the MEP amplitude. Some studies have even demonstrated that PAS may increase GABA-B mediated intracortical inhibition. This has been indicated by increases in CSP duration and increases in LICI (Stefan et al., 2000). Although not statistically significant, effect sizes for main effects of time in our study may suggest similar increases in CSP duration and LICI. Thus, PAS-related increases in GABA-B mediated inhibition may have dampened any potential decreases in GABA-B mediated inhibition from exercise. Implementing a session that included exercise without PAS would have provided valuable insights to the effects of exercise alone on all outcome measures. Having said this, the purpose of this study was to determine how exercise can facilitate neuroplasticity. Removing the plasticity-inducing protocol, PAS, would fail to encompass the primary goal of this study.

Another limitation of the study is that differences in fitness physical activity levels were not controlled for in the analysis. Physically active individuals are more responsive to PAS effects than sedentary individuals (Cirillo et al., 2009). While physically inactive individuals were excluded from participating, fitness levels in physically active participants may have increased variability in outcome measures. Additionally, the means of determining exercise intensity through 60% HRR has its limitations. Factors such as age and resting HR are considered when determining the HR needed for the desired exercise intensity. However, the

trend between HR and fitness levels is not linear. Rather, performing a VO2 max test is considered the gold standard for determining exercise intensity levels. However, when considering the cost-benefit ratio of performing a VO2 max test, calculating the HRR for exercise intensity was more feasible. Since the window for exercise intensities and exercise-induced benefits on plasticity is fairly large, ensuring that individuals are exercising at consistent intensities is not required.

Lastly, the current study used TMS through only one current direction: Posterior-anterior (PA) current direction. The anterior-posterior (AP) TMS current direction can also be used to assess plasticity measures in M1. PA TMS and AP TMS activates unique sets of interneuron input to corticospinal neurons. PA current direction preferentially activates early I waves (I1, I2), whereas AP current preferentially activates later I waves (I3,I4) (Di Lazzaro et al., 2001). Emerging research by Neva (2021) demonstrated that the AP current direction was more sensitive to exercise-induced changes in MEP amplitudes and SICI. This finding suggests that the interneurons recruited from AP current may play a more important role in exercise-induced M1 plasticity. Therefore, it is possible that the current study failed to detect excitability changes that may be present in different sets of interneuron circuits. Since the literature on exercise and AP currents is limited, further research needs to be conducted in healthy individuals before investigating these effects in individuals with a history of concussions.

7.0 Potential Implications and Future Directions

Individuals with a history of concussions have lifelong alterations in M1 neurotransmission. Specifically, longterm increases in GABA-mediated inhibition and decreases in glutamate-mediated neurotransmission has been found. As a consequence of these alterations, synaptic plasticity in the form of LTP and LTD is suppressed. This form of plasticity is critical for the induction of motor learning. In fact, individuals with a history of concussions have been found to show a long-term reductions in implicit motor learning (De Beamont et al., 2012), coordination, ataxia and spasticity (Rabadi & Jordan, 2001). Additionally, motor execution slowness (bradykinesia) has been found in athletes more than three decades after sustaining their last concussion (De Beaumont et al., 2009). These motor symptoms were strongly associated with elevated levels of M1 intracortical inhibition. The accelerated aging model suggests that deficits after concussions may be exasperated as the brain ages. The young brain can compensate for post-concussion alterations through the recruitment of additional brain resources. This process becomes more difficult in the aging brain, as cognitive and motor resources begin to decline. Natural aging is associated with motor cortical atrophy and declines in balance, gait and coordination (Seidler et al., 2010). Sustaining a concussion may further accelerate the rate of these declines. Research has shown that concussions are the most robust environmental Alzheimers disease risk factor in the general population (Heyman et al., 1984). Considering the long-term implications of concussions on brain plasticity, interventions that can restore neurotransmission to pre-concussions levels would be valuable.

Aerobic exercise was used in this study as a means to enhance LTP/LTD-like M1 plasticity. Exercise enhanced M1 neuroplastic markers, as demonstrated by a decrease in GABA-A-mediated neurotransmission. This is an important finding, as decreases in GABA mediated

inhibition is fundamental for the induction of M1 plasticity and motor learning. As such, these decreases may facilitate the induction in LTP/LTD-like plasticity in individuals with a concussion history. On the contrary, exercise failed to alter GABA-B mediated inhibition and glutamate-mediate neurotransmission. Considering that increases in GABA-B mediated inhibition is the most prominent deficit related to M1 plasticity after sustaining a concussion, aerobic exercise may not be the most successful method to restore neurotransmission levels. However, other methods of exercise need to be tested. Adjusting the intensity, mode or duration of exercise may differentially modulate excitability and plasticity of M1. Furthermore, the effects of longterm exercise and M1 plasticity needs to be investigated.

8.0 Conclusion

The current study provides insights into the effects of acute aerobic exercise on the potential for use-dependent plasticity in the motor cortex in individuals with a concussion history. The prominent finding from this study was that exercise enhanced use-dependent plasticity through alterations in intracortical inhibitory netoworks that modulate corticospinal output in M1. This was demonstrated through decreases in GABA-A receptor-mediated intracortical inhibition. Specifically, SICI was reduced when aerobic exercise preceded the plasticity-inducing protocol, PAS, compared to PAS alone. On the contrary, acute aerobic exercise had no effect on enhancing PAS through alterations in GABA-B-recpeptor mediated intracortical inhibition. This was demonstrated through a lack of change in LICI and CSP after exercise, compared to PAS alone. PAS increased corticomotor excitability in individuals with a history of concussions. This was reflected through increases in MEP amplitudes after the exercise + PAS session and the PAS alone session. However, exercise did not further enhance the effects of PAS through enhancing corticomotor excitability. When accounting for overall LTP and LTD-like plasticity, exercise may dampen the effects of PAS through reducing LTP and LTD-like plasticity.

These findings suggest that moderate-intensity aerobic exercise may facilitate intracortical inhibitory networks that are associated with LTP-like plasticity in M1 in individuals with a concussion history. However, exercise does not enhance the potential for use-dependent plasticity in M1 through the enhancement of excitability of corticospinal networks. The combined suggests that exercise may be used as an important consideration for normalizing the long-term M1 alterations that persist after sustaining a concussion. Future research on different

exercise types and intensities should be conducted to gain a further understanding of the benefits of exercise on brain plasticity.

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