CORTICOSPINAL EXCITABILITY ENHANCES WHEN AEROBIC EXERCISE MATCHES

REGULAR PHYSICAL ACTIVITY INTENSITY

by

Brittany S. Roberts

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ABSTRACT

Corticospinal excitability (CSE) increases after a single bout of aerobic exercise (AE), facilitating neuroplasticity. However, while some individuals enhance in CSE after a bout of AE, others show a decrease or no apparent change. This variability may result from the AE intensity being improperly tailored to the intensity of one's regular physical activity (RPA) behaviours. As such the objective of this research study was to determine the influence RPA behaviours have on facilitating CSE after a single bout of AE. The relationship between RPA intensity, assessed using accelerometers, and CSE, assessed using single-pulse transcranial magnetic stimulation, was examined at three different AE intensities (low, moderate, and high) to determine if there was a match between RPA intensity and AE intensity that leads to a change in CSE. We hypothesized greater CSE increases would result when the RPA intensity matched with the AE intensity. Results showed a positive relationship between time spent in vigorous physical activity and CSE, in that CSE increased to a greater extent after the bout of high intensity AE in those participants who spent a greater percentage of time doing vigorous physical activity. No such relationship was observed between time spent in moderate physical activity and CSE or time spent in low physical activity and CSE. These findings improve our understanding of the impact RPA behaviour has on the brain's response to an acute bout of AE, and overall may help in advancing the individualized prescription of AE.

LIST OF ABBREVIATIONS USED

Δ – Change in

a-$\bar{v}$ O_2 difference – Arteriovenous oxygen difference

ACSM - American College of Sports Medicine

ADLs- activities of daily living

AE – Aerobic Exercise

AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AUC – Area Under the Curve

BDNF – Brain- derived neurotrophic factor

CE – cortical excitability

CHMS – Canadian Health Measures Survey

CSE – corticospinal excitability

CVD – Cardiovascular disease

EMG - Electromyography

EE – Energy Expenditure

FDI – First Dorsal Interosseous muscle

GABA - $\gamma - aminobutyric\ Acid$

GXT – Graded maximal exertion test

HR – Heart Rate

HRR – Heart Rate Reserve

HR_{max} – Maximal Heart Rate

IHI – interhemispheric inhibition

IPAQ – International Physical Activity Questionnaire

ISI – Interstimulus Interval

kcal – kilocalories

LICI- long interval intracortical inhibition

LPA – light physical activity

LTP – Long- term potentiation

M1 – Primary Motor Cortex

MEP – Motor Evoked Potential

MET – Metabolic Equivalent

MPA – Moderate physical activity

MT – Motor Threshold

MVPA – Moderate – to – Vigorous Intensity Physical Activity

NHANES – National Health and Nutritional Examination Survey

NMDA – N- methyl – D- aspartate

PA – Physical Activity

PAR-Q – Physical Activity Readiness Questionnaire

PAS – Paired Associative Stimulation

PASBQ – Physical Activity and Sedentary Behaviour Questionnaire

PO – Power Output

PO_{max} – maximal Power Output

rMT – Resting Motor Threshold

RPA – Regular Physical Activity

RPE – Rating of Perceived Exertion

rpm – Rotations per Minute
S-R – Stimulus- Response
SEM – standard error of the mean
SICI- short interval intracortical inhibition
SV – stroke volume
sBDNF – serum brain derived neurotrophic factor
TMS – Transcranial Magnetic Stimulation
VO_2 – volume of oxygen consumption
VO_{2max} – maximal volume of oxygen consumption
VPA – vigorous physical activity

GLOSSARY

Activity counts – a metric used to derive physical activity intensities from an accelerometer

Aerobic capacity – the maximal capacity for the re-synthesis of energy (ATP) aerobically, also referred to as maximal aerobic power.

Aerobic endurance - the ability of the heart, lungs and blood vessels to deliver oxygen to body tissues. The more efficiently the body delivers oxygen to its tissues, the more breathing rate will reduce.

Aerobic exercise – a physical exercise of low to high intensity that depends primarily on the aerobic energy generating processes, stimulating and strengthening the heart and lungs, improving the body's utilization of oxygen (aerobic endurance)

Aerobic fitness - body's ability to uptake oxygen and utilize it to produce energy for your muscle cells to sustain exercise, measured by VO_2max. Factors that influence aerobic fitness include: lung efficiency, cardiac function, gender, age and genetic makeup.

Aerobic metabolism – the production of energy (ATP) in the presence of oxygen within the mitochondria

Angiogenesis - the development of new blood vessels

Arteriovenous oxygen difference – the difference in the oxygen content of the blood between the arterial blood and the venous blood. It is an indication of how much oxygen is removed from the blood in capillaries as the blood circulates in the body

Cortical excitability – the strength of stimulation with cortical neurons, both in specificity and responsivity, both of which are important for neural plasticity

Corticospinal excitability (CSE) – an enhancement in the pathway between cortical neurons, within the cortex, and the spinal cord to a given stimulation, measured by transcranial magnetic stimulation.

Energy Expenditure (EE)– the amount of energy (or calories) needed to perform a physical function, such as breathing, circulating blood, digesting food, or physical movement. Your total daily energy expenditure (TDEE) is the total number of calories you burn each day. Measured in kcals.

Exercise – a type of physical activity that consists of planned, structured, and repetitive movement elicited, with a goal or objective, to improve and/or maintain one or more components of physical fitness.

GABA – an amino acid that acts as an inhibitory neurotransmitter in the CNS, limiting nerve transmission and preventing nervous system activity

Glutamate – a primary excitatory neurotransmitter of the brain that has a role in learning and memory, vital for brain functions.

Health-related physical fitness – components of physical fitness related to health include: cardiorespiratory endurance, body composition, muscular strength, muscular endurance, and flexibility).

Long-term potentiation (LTP) – the permanent enhancement in synaptic transmission and efficacy (>30 mins), and is a primary goal of both motor learning and memory interventions as well as neurorehabilitation following a brain injury.

Neurogenesis - the process by which nervous system cells, the neurons, are produced by neural stem cells, and it occurs in all species of animals except the porifera and placozoans

Neuroplasticity – reorganization of the brain from experiences, forming new synaptic connections and altering brain functioning

NMDA – an amino acid derivative, similar to glutamate

Physical activity (PA)– any bodily movement produced by a skeletal muscle contraction resulting in substantial increases in caloric requirements over resting energy expenditure.

Physical fitness – a set of attributes or characteristics an individual possesses or achieves that relates to their ability to perform physical activity.

serum BDNF – produced by peripheral blood cells which has a larger concentration of BDNF, compared to the plasma, providing an indication of BDNF stored in platelets as well as circulating BDNF in the blood.

Maximal volume of oxygen consumption (VO_2max) – highest rate of oxygen consumption reached during exhaustive exercise, the 'gold standard' to measure aerobic fitness

Motor evoked potential – the quantification of corticospinal excitability when stimulated by transcranial magnetic stimulation (TMS) over the human motor cortex

Priming – a technique used whereby exposure to one type of stimulus influences a response to a subsequent stimulus, without conscious guidance or intention

Resting motor threshold - the minimum stimulus intensity that produced a minimal motor evoked response (about 50 µV in at least 5 of 10 trials) at rest.

Stimulus- response curve - the input-output properties of the corticospinal system, or how MEP size is affected by changes in TMS intensity.

Transcranial magnetic stimulation (TMS) – a non-invasive brain stimulation technique used to measure excitatory and inhibitory processes within cortical neurons

Volume of oxygen consumption (VO_2) - the amount of oxygen consumed by the tissues of the body, usually measured as the oxygen uptake in the lung.

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CHAPTER 1: INTRODUCTION

Engaging in regular physical activity (RPA) can enhance health and promote longevity; the types and amount of RPA is vastly different between individuals, depending on life choices, and can also vary over time within an individual's lifetime, ranging from household chores or walking to the store, to jogging or high intensity training (Caspersen, Powell, & Christenson, 1985). Physical activity (PA) is defined as any movement performed by the skeletal muscles resulting in an increase in energy expenditure (EE; Saunders, Greig, & Mead, 2014). The amount of EE required to perform a task is measured by kilocalories (kcal) per unit of time, a continuous variable ranging among individuals from low to high (Caspersen et al., 1985). Daily or weekly measures are common units of time used for EE (Paffenbarger, Wing, & Hyde, 1995). The energy expended for a given PA is commonly expressed in relation to the amount of oxygen consumed at rest while sitting (3.5 mL VO_2/kg body weight/ min) or one metabolic equivalent of the task (MET; Jette, Sidney, & Blumchen, 1990). Thus, below 3 METs is considered to be low physical activity (LPA), greater than 3 METs is considered moderate physical activity (MPA), and greater than 6 METs is considered vigorous physical activity (VPA; Nang et al., 2011). These categories of PA intensity differ based on the intensity, duration, and frequency of the muscular contractions as the amount of muscle mass producing the bodily movement determines the energy expended (Caspersen et al., 1985). When PA is of a moderate-to-vigorous intensity, significant health benefits result (Hagstromer, Oja, & Sjostrom, 2006). The Canadian Society for Exercise Physiology (CSEP) currently states that adults (18-64 years of age) should accumulate 150 minutes per week of moderate-to-vigorous PA (MVPA) that is aerobic in nature (i.e., use of oxygen or the cardiovascular system through activities such as walking, biking, or jogging), in

order to meet PA guidelines. Meeting this guideline improves health by reducing risks of cardiovascular disease (CVD), cancer, stroke, type 2 diabetes, osteoporosis, and hypertension, as well as improving fitness and body composition (CSEP, 2018). When these guidelines are not met, the individual is considered 'physically inactive', and can contribute to developing CVD and overall poorer health status (Dustan et al., 2010). Physical inactivity is a lack of being physically active. It is important to distinguish physical inactivity from being sedentary (or engaging in sedentary behaviours (SB; e.g., lying or sitting), which occurs when EE falls below 1.5 METs. This distinction between physical inactivity and SB is important, as an individual can be categorized as being physically active (i.e., they could meet the CSEP guidelines), yet engage in a considerable amount of SB. This thesis examines RPA behaviour and CSE, and thus does not focus on SB. Given the positive effects of engaging in PA, clinicians and other health care providers encourage a physically active lifestyle to reduce the risk of developing poor health status as RPA can reduce the likelihood of developing chronic diseases as well as cognitive decline later in life (Macpherson, Teo, Schneider, & Smith, 2017).

The vast majority of studies use self-report questionnaires to quantify the intensity, duration, and frequency of PA an individual engages in over a 7-day period, such as the International Physical Activity Questionnaire (IPAQ). However, it is evident that this method of quantifying PA has limitations, such as social desirability and memory biases, resulting in inaccurate quantification of EE (Brocklebank, Falconer, Page, Perry, & Cooper, 2015). Since individuals tend to over-report PA (Dannecker, Sazonova, Melanson, Sazonov, & Browning, 2013), this study used accelerometers to record minute-by-minute body movements as well as postural allocations that help to identify sedentary time (i.e., sitting, lying, and standing; Sazonov, Fulk, Hill, Schutz, & Browning, 2011), to gain a more accurate and precise measurement of the

amount and characteristics of RPA (i.e., duration and intensity) in order to determine the relationship RPA has on CSE. Time spend sedentary was also assessed in an attempt to better characterize the study population.

To understand the impact that various forms of activity have on the body, it is important to first define what they mean, as the terms 'physical activity', 'exercise', and 'physical fitness', are often used interchangeably despite them being considered separate concepts (Caspersen et al., 1985). PA refers to body movements that expend energy, which can vary from low to high intensity. Exercise, a subset of PA, is planned and structured, and repeatedly performed to maintain or improve health as well as certain components of physical fitness (Caspersen et al., 1985). AE is planned, structured, and repetitive form of exercise that can alter in intensity, duration, and frequency to improve or maintain components of health-related physical fitness. There are five components of physical fitness that are related to health: aerobic endurance, muscular endurance, muscular strength, body composition, and flexibility (Caspersen et al., 1985). Aerobic endurance reflects the ability of the cardiovascular and respiratory system to supply the working muscles with oxygen. AE involves dynamic MVPA that is maintained for an extended amount of time in an attempt to strengthen the cardiovascular and respiratory systems; improving aerobic endurance and overall health (Pescatello & American College of Sports, 2014). Thus, improving aerobic endurance will improve aerobic fitness, the ability of the working muscles to utilize oxygen to produce energy for movement (Kenney, Wilmore, & Costill, 2012, p. 249). Additionally, moderate to high aerobic fitness levels have been recommended for effectively reducing the risk of age-related declines in physical and cognitive functioning, thus some studies provide evidence of improved physical and cognitive functioning after an AE training intervention in older adults (Paterson & Warburton, 2010).

Typically, studies use moderate intensity AE, typically defined as 60-70% of maximal heart rate (HR_{max}) or 40-50% HR reserve (Pescatello & American College of Sports, 2014), to elicit improvements in physical and cognitive functioning (McDonnell, Buckley, Opie, Ridding, & Semmler, 2013; Mooney, Coxon, Cirillo, Glenny, Gant, & Byblow, 2016; Smith, Goldsworthy, Garside, Wood, & Ridding, 2014); however, there are difficulties with using AE to improve functioning as the intensity and amount of AE facilitating these improvements varies among individuals and with different methodologies used (Paterson & Warburton, 2010). Studies that have investigated the role AE has on improved physical and cognitive functioning suggest that AE has positive effects on numerous body systems and functions (Hu & Lin, 2012), with growing evidence of AE training benefiting brain health (e.g., learning, memory, and cognition; Statton, Encarnacion, Celnik, & Bastian, 2015).

Although PA, physical fitness, and exercise are separate concepts (Caspersen et al., 1985), all have been associated with beneficial changes in brain structure and function (Kramer & Erickson, 2007). Compared to anaerobic training, engaging in three one- hour AE training sessions each week, over six months, elicited changes in brain structure evidenced by increased grey and white matter volume in the prefrontal and temporal cortex, which house regions responsible for learning (supplementary motor area; SMA) and memory (hippocampus) (Colcumbe & Kramer, 2006). Arising from findings of reduced brain volume (Raz et al., 2005), blood flow (Chen, Rosas, & Salat, 2011), and oxygen metabolism changes (Dennis & Cabeza, 2008) that have been shown to occur with age, a vast amount of studies have continuously emphasized the important role AE has on preventing age-related decline in brain function as well as preventing the deterioration of brain tissue that occurs with age (Peters, 2006 for review Raz, 2000; Voss et al., 2016).

The notion that AE can be used to alter the excitability of the brain has potential implications in a number of fields, such as rehabilitation, skill acquisition and skill retention, as well as training effects on performance. Heightened CSE, especially when repetitive, allows for easier and faster activation of a postsynaptic neuron, strengthening the synaptic connections, as well as synchronization, between the neurons via long-term potentiation (LTP), the mechanism underlying learning and memory (Griffin & Cafarelli, 2007). Thus, AE creates an optimal environment for short- and long-term changes to occur within the brain (i.e., brain plasticity), a process known as priming. Owing to this priming effect, AE can be performed prior to a specific motor, or cognitive, task to create an ideal environment in the brain for facilitating the learning of new skills, as well as rehabilitation post brain injury (Singh, Neva, & Staines, 2014a).

In general, changes in CSE resulting from AE can be assessed with transcranial magnetic stimulation (TMS), providing an indication of the effect of AE on brain function and short-term plasticity. Studies that use this method of measuring motor cortex (M1) excitability have shown increased CSE after a single bout of AE (MacDonald et al., 2019) as well as with chronic AE (Cirillo, Lavender, Ridding, & Semmler, 2009).

Although a single bout of AE has been shown to elicit increased CSE and other indices of short-term plasticity, there is considerable variability in the CSE response to AE across individuals (Zanette et al., 1994; Cirillo et al., 2009; Lulic, El-Sayes, Fassett, & Nelson, 2017). The variability in the effect of AE on CSE is suggested to be a result of differences in prior PA levels, as well as inconsistencies in the dosage of AE given (Colcumbe & Kramer, 2003). To date, limited studies have investigated how individual differences in patterns of RPA contribute to the variability observed in CSE after an acute bout of AE. There has been even fewer studies that have compared various intensities of RPA, including LPA, MPA, and VPA, on CSE

responses after AE. However, characterizing and measuring the intensity of RPA varies among studies, which may also account for the differences in CSE among individuals within the same RPA group after a single bout of AE. Thus, this study aims to determine if greater increases in CSE are elicited after a single bout of AE when the intensity of the AE is the same as the intensity of the RPA the participant typically engages in, where RPA intensity is defined as the duration of time spent in LPA, MPA, and VPA. More specifically, higher CSE would be shown after high intensity AE among individuals with more duration of time spent in VPA, after moderate intensity AE among individuals with more duration of time spent in MPA, and after low intensity AE among individuals with more duration of time spent in LPA.

Examining the role RPA intensity has on CSE after AE requires accurate measurements of RPA in order to improve understanding of the influence RPA has on CSE. Subjective measures such as self-reports are used to assess PA, but these subjective measures fail to capture and characterize RPA accurately (Sallis & Saelens, 2000). Specifically, individuals could potentially meet the guidelines for MPA or VPA by engaging in frequent and long durations of walking (i.e., LPA) as self-reported questionnaires, such as the IPAQ, calculate a total PA score by multiplying frequency and duration of walking, MPA, and VPA by a standardized MET value. If this MET value is above 600 MET minutes per week then the total PA score is identified as MPA, whereas if the MET value is above 1500 MET minutes per week the total PA score is identified as high PA (IPAQ, 2005). Unlike subjective self-report, objective measures, such as accelerometers, provide a more accurate and complete measure of RPA, and thus are a preferable means to examine the influence RPA has on the cortical response to an acute bout of AE. Accelerometers are preferable for assessing RPA as they directly reflect the duration and intensity of an activity bout, including periods of inactivity, whereas self-report questionnaires

cannot. These differences in RPA intensity are distinguished by the number of activity counts within an epoch of activity, or inactivity, with higher activity counts reflecting higher intensities of PA; thus, the activity counts have a linear relationship with the PA intensity during that epoch of time (Santos-Lozano et al., 2013). The activity count cut offs for each PA intensity, as well as SB, are determined from calibration studies as well as the manufacturer of the accelerometer (Romanzini, Petroski, Ohara, Dourado, & Reichert, 2014; explained further in section 2.6).

As previously mentioned, AE can drive increases in CSE, which in turn creates an optimal environment for longer-term plasticity to occur. However, recent research has shown that individuals with lower levels of PA may not show as much of an increase in CSE than their age-matched counterparts with higher PA levels (Lulic et al., 2017). A recent study showed participants with higher levels of PA, indicated by self-reports on the IPAQ, had increased CSE after a 20-minute bout of moderate intensity AE compared to lower levels of PA (Lulic et al., 2017). While this previous study did show a difference in the CSE based on PA level, considerable variability was present, with some individual participants within the same PA level (e.g., high) showing the opposite effect or no change in CSE after AE. It is also possible that the variability in the responses is attributable to the use of the IPAQ to quantify RPA levels.

Since previous studies have shown inconsistencies in the CSE response among individuals classified as the same RPA level with self-reported measures of RPA after a single bout of AE, leading to an unknown influence of RPA on CSE, here, we investigated whether these different responses in CSE are the result of individual differences in the intensity of RPA the individual typically engages in. Furthermore, we aimed to explore if the variability in the individual's percent change in CSE ($\%CSE_{change}$) to a single bout of AE was the result of a discrepancy between the AE intensity used relative to the duration spent in LPA, MPA, and VPA. Said

another way, we explored if the %CSE$_{change}$ to a single bout of AE would be optimized if the intensity of the AE matched the intensity of the RPA the individual typically engaged in. Thus, we examined the relationship between RPA intensity, measured by accelerometers, and CSE after low, moderate, and high intensity AE to determine whether optimal CSE at a given AE intensity matches the individual's percent wear time in LPA, MPA, and VPA (i.e., the percentage after normalizing the average minutes per day across the number of valid days). We predicted that CSE would increase after the AE bout when the individual accumulated higher percentage wear time in the same intensity of RPA as the AE intensity, compared to the AE intensity that is not the same. Thus, higher accumulated percent wear times in VPA would show enhanced CSE after high intensity AE; higher accumulated percent wear times in MPA would show enhanced CSE after moderate intensity AE, and higher accumulated percent wear times in LPA would show enhanced CSE after low intensity AE. This research aimed to improve knowledge related to the effects of AE on brain function and short-term plasticity as well as the individual characteristics, such as RPA, that influence this relationship.

CHAPTER 2: BACKGROUND

2.1 Impact of Regular Physical Activity on Health

2.1.1 *Regular Physical Activity and the Peripheral Nervous System.* Engaging in RPA alters various body systems and functions. The autonomic nervous system (ANS), which controls involuntary internal functions within the motor division of the peripheral nervous system (PNS; e.g., HR, blood pressure, blood distribution, and lung function), alters during PA. The ANS is also responsible for preparing the body for action via the sympathetic nervous system (SNS). The functions of the SNS that are activated during PA include increases in heart rate and strength of cardiac contraction; blood supply to the heart; peripheral vasodilation which increases blood flow to active skeletal muscles; vasoconstriction in inactive areas to provide blood to the active muscles; blood pressure which increases blood perfusion to the muscle and improves the return of blood to the heart; bronchodilation for improved ventilation and gas exchange; metabolic rate to meet the increased demand of PA; mental activity which improves perception of sensory stimuli and concentration; and blood glucose released from the liver for energy. The PNS also helps increase heart rate by reducing activity to the SA node of the heart. Thus, the ANS has a significant role in altering body functions to elicit motor responses and maintain acute PA (Kenney et al., 2012, pg. 72).

There are many well-documented effects of engaging in higher intensities of RPA, such as increased stroke volume (SV) and blood flow to the brain (Petriz et al., 2016), as well as elevated levels of muscle contractile proteins (Egan & Zierath, 2013). Enhanced SV, the amount of blood pumped by the heart per contraction, can occur when HR increases (Blomqvist & Stone, 1983). Thus, more blood is ejected from the heart, resulting in increased blood supply to the

brain and in turn greater amounts of nutrients and substrates such as glucose and oxygen, which are necessary for sustaining upregulated brain function.

2.2   Effect of Regular Physical Activity on the Brain

Over the past 40 years research has indicated RPA can have neuroplastic and neuroprotective effects on the human brain (Smith, Erickson, & Rao, 2015). For instance, studies in older adult populations have provided insight as to how frequent PA can reduce the risk of cognitive impairments (Laurin, Verrault, Lindsay, MacPherson, & Rockwood, 2001). Erickson and colleagues (2010) compared older adults who were more physically active to those less active as defined by self-reported duration and frequency of walking on the Minnesota Leisure-Time Activities Questionnaire. Individuals with longer duration (i.e., more blocks walked) and more frequent walking over one week were classified as performing higher levels of PA. This study was a longitudinal study design that examined changes in grey matter volume nine years after initial baseline assessments of PA. They found greater grey matter volume in the prefrontal and temporal areas among those who walked more, reaching 72 blocks or 6-9 miles per week (see Figure 1), specifically within the supplementary motor area (SMA), hippocampus, left precentral gyrus, and precuneus brain areas (see Figure 2).
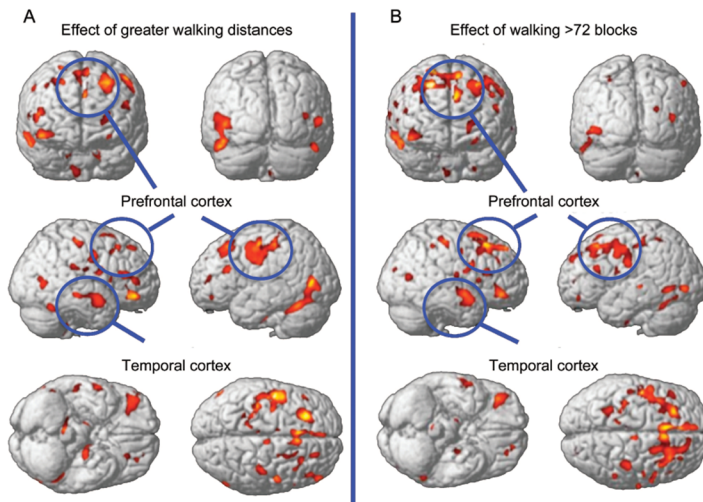
Figure 1. Prefrontal and temporal brain regions associated with longer duration and more frequent walking. (A) Brain areas showing an association between greater amounts of physical activity (blocks walked) at baseline and greater gray matter volume. Statistical map is thresholded with a false discovery rate of p = .05 and a minimum cluster threshold of 100 contiguous voxels. (B) Brain areas showing greater volume in the highest quartile (>72 blocks walked in 2 weeks) compared to the bottom 3 quartiles. There were no reliable differences in brain volume among the bottom 3 quartiles. (Erickson et al., 2010).
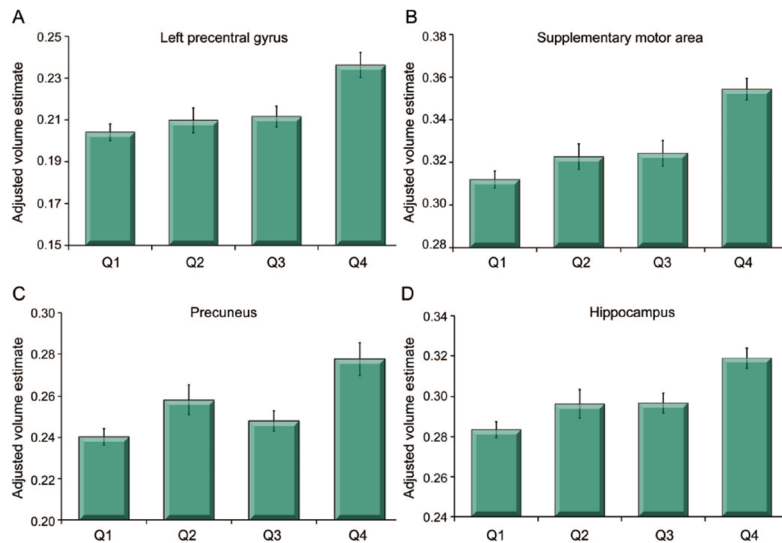
Figure 2. Physical activity threshold effects on brain volume. Average volumes of the (A) left precentral gyrus, (B) supplementary motor area, (C) precuneus, and (D) hippocampus, adjusted for variance due to age, total intracranial volume, gender, body mass index, race, white matter grade, presence of MRI infarcts, and education split into quartiles based on the amount of physical activity (Q1: 0-12 blocks, n = 91; Q2: 13-24 blocks, n = 57; Q3: 25-70 blocks, n = 78; Q4: 72-300 blocks, n = 73). The highest quartile group (Q4) had greater volume in all regions examined compared with the lower 3 quartiles. No significant differences were found among the lower 3 quartiles. Error bars indicate standard error of the mean (SEM; Erickson et al., 2010).

Therefore, Erickson and colleagues (2010) provided evidence that PA helps to preserve brain areas that are most prone to age-related atrophy. Further, the brain areas showing greater volumes of grey matter with greater amounts of PA were correlated with a diminished risk of a clinically determined cognitive decline (i.e., dementia or mild cognitive impairment) at follow-up 13 years after the initial baseline measurement of PA (Erickson et al., 2010). Although a causal relationship cannot be deduced from this study, there were ~300 older adults from 70 - 90 years old (M = 78 years old) who were involved with the study for nine years (1989-1998) which gives the study considerable power and significance (Field, 2013).

In light of the notion that RPA can change brain activity and enhance brain plasticity (Cirillo et al., 2009), studies have compared individuals with more RPA to those with lower

levels of RPA on a given motor task. For instance, McGregor and colleagues (2011) provided evidence that sedentary older adults show a different pattern of brain activity during a finger tapping task compared to their more physically active counterparts using a non-invasive brain stimulation technique known as transcranial magnetic stimulation (TMS) and the blood oxygen level dependent (BOLD) signal from functional MRI (fMRI). The sedentary older adults, determined by self-reported PA levels on the Weekly Leisure Activity Survey combined with a 12-minute treadmill test, activated the right M1 in addition to the left M1 during a tapping task using the right index finger whereas the more physically active older adults primarily recruited the left M1 (McGregor et al., 2011; see Figure 3). Additionally, motor evoked potentials (MEP) elicited from the the 'hand knob' of the right M1 using TMS during the finger tapping task showed were of reduced amplitude among the sedentary older adults, thus indicating lower levels of brain excitability (i.e., CSE), compared to physically active older adults and young adults. The results suggest that greater amount of PA resulted in altered brain function among the older adults, who showed similar brain activation patterns to the younger adults during the finger tapping task, while their less physically active age-matched counterparts did not (McGregor et al., 2011).
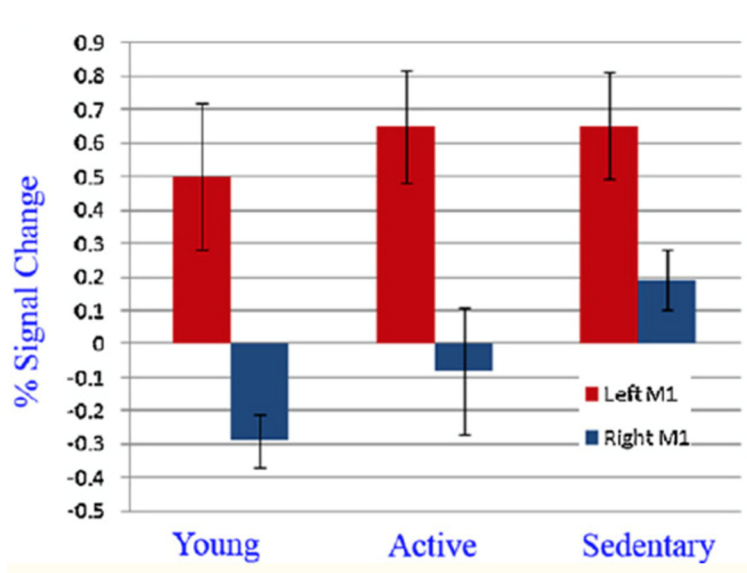
Figure 3. Comparing hemodynamic response between sedentary older adults, physically active older adults, and young adults during tapping task. Bar graph indicates significant differences (p <.01) in the average percentage of the signal change of estimate of hemodynamic response from primary motor areas (M1) between each group during motor tapping task. Higher bars indicate greater change in signal change on average for each group: right M1 (blue) and left M1 (red). The younger and active older adults showed decreased signal change from baseline compared to sedentary older adults who showed increased signal change from baseline in the right M1. Error bars reflect standard deviation. (McGregor et al., 2011).

Similar evidence is shown among younger adults, with individuals self-reporting higher amounts of PA showing significantly higher functional connectivity (i.e., connections between regions in the brain) compared to individuals reporting less PA (Raichlen et al., 2016). Specifically, the individuals reporting higher amounts of PA (in this instance endurance athletes) showed greater functional connectivity between the right SMA and the left frontoparietal network, reinforced by the significant positive correlation between the connectivity and MET values (see Figure 4).
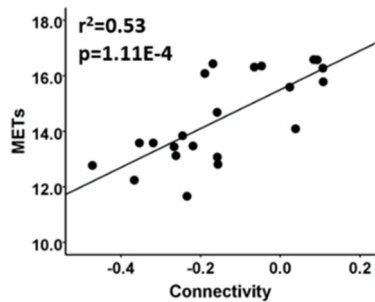
Figure 4. Difference between frontoparietal network connectivity at rest among athletes and non-athletes. The scatterplots show the positive relationship between the connectivity between the supplementary motor area and the frontoparietal network and the MET value. (Raichlen et al., 2016).

The aforementioned studies provide evidence that engaging in RPA can elicit neuronal changes, both in structure and function, also known as experience-dependent plasticity (Kempermann et al., 2010). As indicated previously, RPA encompasses various types of activities that range from low intensities (incidental PA, most household chores, slow walking) to moderate-vigorous intensities (brisk walking, jogging, cycling, sports), however, activities that are moderate-vigorous in intensity (e.g., MVPA) that are aerobic in nature are recommended to elicit health benefits (Thornton et al., 2016). The RPA adaptations on the body and brain can also be facilitated, as well as be dependent on, various combinations of intensities and durations of PA (Kenney et al., 2012, pg. 453). Aerobic exercise is a common type of PA that is clinically implemented to enhance brain plasticity, as well as learning and memory, as it elicits a cascade of neural changes (Mang, Campbell, Ross, & Boyd, 2013), both structurally and functionally (Singh et al., 2014a). The 'gold standard' to analyze these neural changes in M1, specifically the excitatory and inhibitory intra- and inter-cortical networks responsible for LTP underlying learning and memory is TMS (explained in detail below).

2.3   Corticospinal Excitability

The nervous system has countless numbers of neurons and synapses that make up complex neural circuits, which are involved in eliciting behaviors (Walinga, 2012). Neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA), and their corresponding receptor on the neuron cell membrane are responsible for the level of excitability within the brain (excitation or inhibition). Cortical excitability (CE) is the strength of the response of neurons within the cortex to a given stimulation, reflective of neuron reactivity and response specificity, which are both fundamental aspects of human brain function. Glutamate acts on N-methyl-d-aspartate (NMDA) receptors, as well as non-NMDA receptors (e.g, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or AMPA, receptors), mediating excitation, whereas GABA acts on $GABA_A$ and $GABA_B$ receptors mediating inhibition (Badawy, Loetscher, Macdonell, & Brodtmann, 2012). Glutamate is robustly upregulated in response to a single, acute session of vigorous AE at >80% age-predicted HR_{max} (Maddock, Casazza, Fernandez, & Maddock, 2016). Upon release from the pre-synaptic terminal, glutamate activates AMPA receptors on the post-synaptic cell membrane, as magnesium ions (Mg^{2+}) block NMDA receptors at rest, causing sodium ions (Na^+) to pass through the AMPA receptor, depolarizing the cell (Figure 5a). This cascade of events can cause LTP, the enhanced strength of a synapse that facilitates learning and memory, only if a high amount of repeated stimulation occurs (Albright et al., 2000; Kandel, Schwartz, & Jessell, 2000). When there is a large stimulation of the AMPA receptors, causing more Na^+ to enter, the Mg^{2+} blocking the NMDA receptor is removed via electrostatic repulsion, allowing calcium ions (Ca^{2+}) to flow into the post-synaptic cell (Figure 5b). Calcium is an important secondary messenger that elicits secondary intracellular cascades, inducing LTP. These intracellular cascades include the

insertion of new AMPA receptors into the membrane of the post-synaptic neuron at an active

synapse, as well as phosphorylating AMPA receptors enhancing glutamate sensitivity via

Ca^{2+}/calmodulin-dependent protein kinases. Further, these processes result in an increase in

glutamate release (stimulated by retrograde messengers) from the pre-synaptic cell (Kandel et al.,

2000). Through these events at the pre- and post-synaptic membrane, direct neural pathways and

connections become stronger and enhances the optimal neural environment for learning.
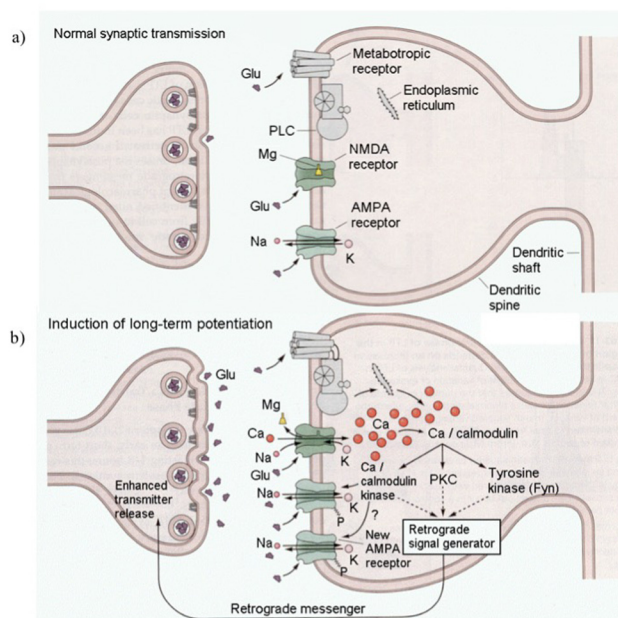
Figure 5. Induction of long-term potentiation. (a) During normal synaptic transmission glutamate (Glu) is released from the pre-synaptic terminal and acts on the NMDA and AMPA receptors in the post-synaptic neuron. Sodium (Na) and potassium (K) flow in and out of the AMPA receptor, respectively. The NMDA receptor ion channel is blocked by magnesium (Mg). (b) Long-term potentiation is induced by the influx of calcium (Ca) and a cascade of intracellular signaling. (Kandel et al., 2000).

As neuroplasticity is a pre-requisite for learning, which in turn forms the basis for

recovery of motor and cognitive function afte brain injury such as stroke (i.e., functional

recovery), methods that alter the resting membrane potential of neurons within the cortex (and

more precisely moving them closer to the threshold for depolarization) prior to engaging in a

rehabilitation intervention have been investigated. Some of these methods include resistance exercise, aerobic training (Gardiner, Dai, & Heckman, 2006), caffeine, as well as non-invasive brain stimulation (e.g., TMS).

The changes in nervous system excitability resulting from a single bout of AE can be assessed using TMS through CSE, which encompasses activity of the various neurotransmitters at the level of the cortex through the spinal cord as cortical neurons synapse with alpha motor neurons within the ventral horn of the spinal cord (i.e., the corticospinal tract). Measuring CSE before and after an intervention provides an index of excitability that is altered by said intervention (Badawy et al., 2012). Given the role of AE in increasing CSE, it is thought to be a promising technique in rehabilitation, specifically stroke rehabilitation (McGregor et al., 2011). With the increase in knowledge of the benefits of exercise on body systems and brain function, specifically AE, many studies have implemented AE prior to a physical or cognitive task to examine improvements in brain functioning (and resultant behaviour) due to AE. This process, known as priming, is useful in rehabilitation to improve brain function and processes related to learning and memory, as well as brain recovery. As previously mentioned, TMS is used primarily to assess CSE.

2.4   Transcranial Magnetic Stimulation

As indicated above, increasing CSE can make it more likely that a given neuron will be depolarized, thus increasing the likelihood of driving LTP and in-turn enhancing processes such as learning. Before exploring the effect that AE has on CSE, it is important to first understand how changes in CSE can be assessed. The primary means of assessing CSE is via TMS. Briefly, TMS works by delivering an electric current into the brain induced through the generation of a magnetic field (see Figure 6 and refer to Griskova, Hoppner, Ruksenas, & Dapsvs, 2006

reference for a summary). The induction of an electrical current in M1 results in an action

potential (i.e., depolarization) within the descending corticospinal tract neurons (i.e., those

projecting from M1 to motor neurons in the spinal cord), to a muscle within the stimulated M1

representation, which leads to synchronous muscle activation (i.e., twitch). When coupled with

surface EMG overlying the target muscle, the summation of the resulting action potentials (i.e.,

activation of the muscle) is referred to as an MEP, the amplitude of which reflects the integrity

and excitability of the entire corticospinal pathway (Klomjai, Katz, & Lackmy-Vallee, 2015; see

Figure 7).
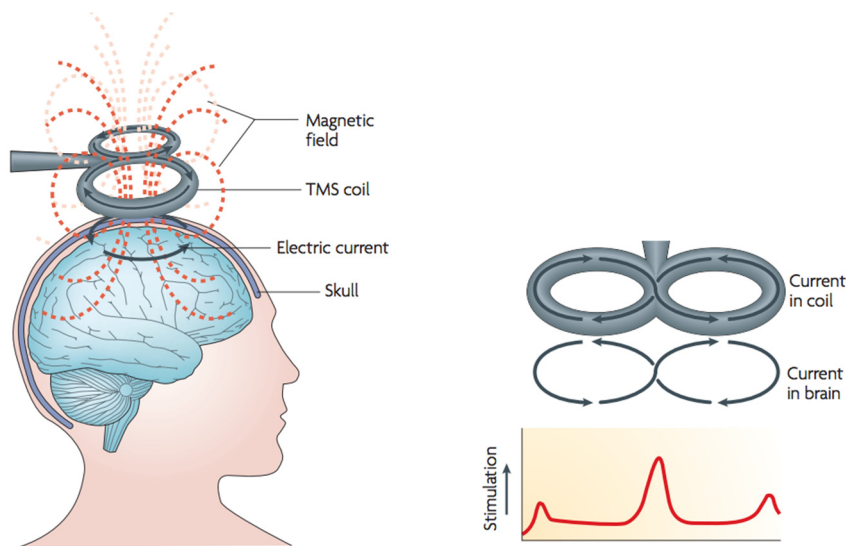
Figure 6. TMS figure-of-eight coil is placed on a small region on the scalp and the electric
current traveling through the coil generates a magnetic field, which in-turn generates a second
electrical current that is transmitted into the cortex eliciting a response (Ridding & Rothwell,
2007).

Simplified scheme of mechanism of action of TMS of the motor cortex
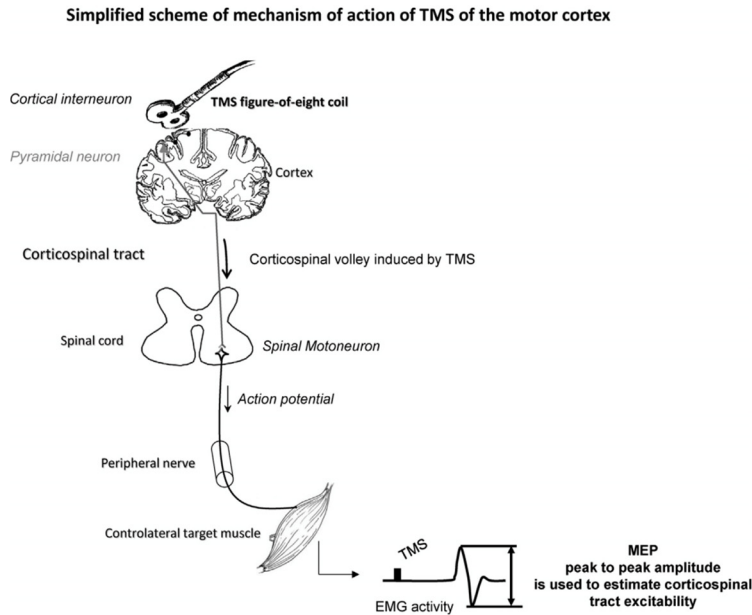
Figure 7. TMS mechanism of action. After cortical interneurons are stimulated within M1, the resulting action potentials traverse the descending corticospinal tract and peripheral nerve, eliciting a contraction in the contralateral muscle. The peak – to – peak amplitude of the resulting MEP provides an estimate of the excitability of the corticospinal tract (Klomjai et al., 2015).

2.4.1 Single-pulse-TMS. While many forms of TMS are available (see Shin et al., 2012 for review), changes in short-term plasticity induced by AE are most often examined using single-pulse techniques. Single-pulse TMS is a method whereby single pulses are delivered to a target region in M1 to generate a MEP in the corresponding muscle (Badawy et al., 2012). Each TMS pulse stimulates glutamatergic (excitatory) neurons (Huerta & Volpe, 2009). When these single pulses are delivered at different intensities of an individual's resting motor threshold (rMT, the lowest intensity of stimulator output required to elicit a MEP of >50µV peak-to-peak amplitude on 5/10 trials), typically between 100-140% of rMT, the excitability of the corticospinal tract can be determined (i.e., CSE). The relationship between the various TMS intensities and the resulting MEP amplitude, known as the stimulus-response (S-R) curve, is a sigmoid function (see Figure 8, Hanakawa et al., 2009).
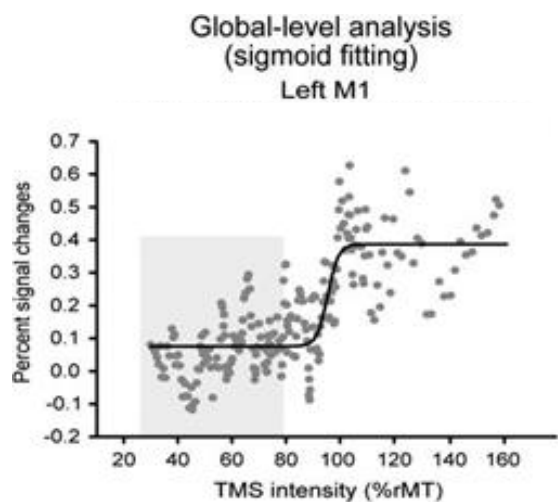
Figure 8. Percent signal change by TMS intensity. The global-level analysis of S-R profiles as fitted with a sigmoid function. Stimulus intensity is expressed as the physiological intensity (% rMT) of TMS stimulation, with the gray dots representing a single data point from each stimulus-intensity condition from each participant. (Hanakawa et al., 2009)

The rising slope to the flat portion of the sigmoid S-R curve relate to the optimal TMS intensity to determine CSE (Temesi, Gruet, Rupp, Verges, & Millet, 2014). Studies have indicated that 110% and 120% rMT, the most frequently used intensities, are the rising parts of the curve and thus are the most sensitive in detecting a change in CSE as they are less likely to show a floor or ceiling effect (Cuypers, Thijs, & Messen, 2014). In addition, previous research suggests that stimulation over 135% results in no additional increase in normalized MEP amplitude and recruitment of direct corticospinal pathways are favored at stimulation intensities between 120-135% (Pellegrini, Zoghi, Jaberzadeh, 2018). Further, the variability in response is reduced between 120-135% rMT due to the MEP amplitude reaching a ceiling point (Pellegrini et al., 2018). Therefore, 110, 120, and 130% are less likely to experience a floor or ceiling effect (Cuypers et al., 2014) and have a greater reliability of inducing MEP amplitudes (Vaseghi et al., 2015). Since previous research has indicated that there is no difference between 110% and 120%

rMT (Cuypers et al., 2014), and the typical intensity to elicit a MEP is 120%, this study employed a stimulation intensity of 120% to assess changes in CSE.

Singh and colleagues (2014b) recorded MEPs from the extensor carpi radialis (ECR) following a single bout of cycling on a cycling ergometer at a moderate intensity, defined as 65-70% age predicted HR$_{max}$, for 20 minutes. They did not find significant differences in the CSE of the hand region of M1 immediately after the single bout of exercise. However, they did find an enhanced amplitude of the MEP in the ECR at each stimulus intensity (Figure 9).
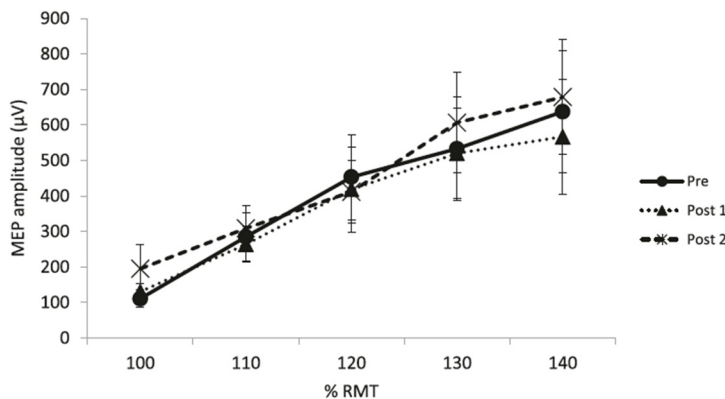
Figure 9. Recruitment curves before and after exercise. S-R curve pre-exercise (circle line), immediately post-exercise (triangle line, and 30 minutes post- exercise (star line). MEP amplitudes increase as stimulus output as a percentage of resting motor threshold (%RMT) increases. Bars indicate the SEM. (Singh, Duncan, Neva, & Staines, 2014b).

Although this study shows CSE after M1 stimulation increases after a single bout of moderate intensity AE (Singh et al., 2014a), most studies show variability in CSE (Singh et al., 2014a; Singh, Neva, & Staines, 2016; Lulic et al., 2017) or no changes in excitability (Smith et al., 2014). There are similar inconsistencies in the literature regarding CSE after high intensity AE, where some studies show increased CSE after M1 stimulation (Mang et al., 2014), whereas others show no change (Stavrinos & Coxon, 2017). Previous research provided statistical evidence that AE intensity is the greatest, and most significant, predictor (shown by the greater F

value) compared to duration and frequency, for improving individual characteristics such as aerobic capacity (Davis & Knibbssee, 1971; see Table 1). Thus, the variance in CSE responses after different AE intensities may be attributed to the AE intensity not being correct for the individual as the AE intensity given will either be too high or too low for the individual, resulting in a suboptimal environment to facilitate changes in the brain (i.e., excitation, inhibition via changes in the concentration of neuromodulatory agents such as glutamate, lactate, BDNF, etc). For example, when AE intensity is too high, blood lactate increases may prevent changes in CSE from occurring (Moscatelli et al. 2010). Thus, in prescribing the intensity of AE, it may be important to consider individual characteristics or experiences, such as the person's RPA behaviours. This, in turn, may result in the production of an optimal neurochemical environment to facilitate positive changes in brain function and in-turn improvements in process such as learning and memory.

Table 1. Co-variance between exercise training factors. Analysis of co-variance of factors contributing to VO_{2max} on a bicycle ergometer, F values and statistical significance (Davis & Knibbssee, 1971).

Variable	F value
Duration (D)	6.75[a]
Frequency (F)	0.11
Intensity (I)	12.47[a]
I × D	5.28[a]
I × F	1.94
D × F	0.59

[a] $p = 0.05$.

2.5   Individual differences and corticospinal excitability

2.5.1   Aerobic Fitness and CSE. The variability in CSE observed after a single bout of AE seen in previous studies may be the result of participant characteristics, such as the aerobic fitness level of the participants, engaged in the research. From studies of older adults, it is known that, compared to older adults with lower aerobic fitness, aerobically fit older adults show larger hippocampal volumes, improving spatial memory performance (Erickson et al., 2011), as well as protection from deterioration of the prefrontal and temporal cortices; brain regions that are associated with executive function and memory (Chieffi, Iavarone, Viggiano, Monda, & Carlomagno, 2012). These adaptations were associated with reduced cognitive decline and risk of age-related neurodegeneration and diseases, such as Alzheimer's and dementia among older adults who had higher aerobic fitness (Larson et al., 2006). However, this study was conducted as prior research had not investigated the impact of an individual's fitness level on CSE after a single bout of AE.

Maximal voluntary consumption of oxygen (VO_{2max}) is the 'gold standard' to determine aerobic capacity (Heyward & Gibson, 2014) as the rate of work increases linearly with the increase in the consumption of oxygen until the individual cannot reach a higher work rate; and thus, is a direct measure of aerobic fitness. The VO_2max test involves the use of specialized equipment that measures breath-by-breath oxygen consumption. The intensity of AE can be prescribed using reported rating of perceived exertion (RPE) on the Borg scale (Heyward & Gibson, 2014; see Appendix 10) and/or as a percentage of participant's HR_{max}. According to the American College of Sports Medicine (ACSM) guidelines (Pescatello & American College of Sport, 2014) RPE can be used to monitor and prescribe exercise intensity as it strongly correlates

with VO$_2$ as well as with HR, among sedentary young adults. The majority of studies use the

Graded Maximal exertion test (GXT), an incremental exercise test, to obtain these values.

To probe one of the possible participant-level characteristics influencing the variability in

CSE response to AE, MacDonald and colleagues (2017) investigated the relationship between

the level of aerobic fitness and CSE after a single bout of AE using single-pulse TMS. The

change in CSE was assessed using the S-R curve, and VO$_{2max}$ was measured using breath-by-

breath analysis. There results showed no relationship between the change in CSE and VO$_{2max}$

(see Figure 9) following a single, 20-minute, bout of AE performed at 50% of the individuals HR

reserve (or ~70% HR$_{max}$; MacDonald, 2017).
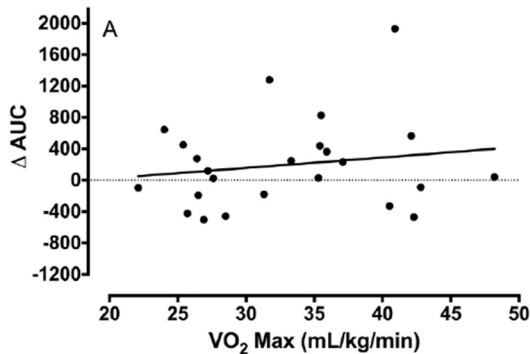
Figure 10. Relationship between CSE and aerobic fitness. CSE (analyzed via area under the curve; AUC) was not significantly influenced by the level of aerobic fitness immediately after a 20- minute bout of moderate intensity AE (MacDonald, 2017).

In addition to their findings related to aerobic fitness, MacDonald et. al., (2017) reported

a weak positive relationship between self-reported IPAQ scores (MET minute per week) and

VO$_2$max scores (see Figure 11). Given only IPAQ scores were obtained, the work by MacDonald

et. al., did not obtain an accurate portrayal of the RPA that an individual engages in, limiting

conclusions that can be drawn from this work related to RPA and the response to a single bout of

AE. Previous studies show varied results, from no relationship (Benedict et al., 2012) to a

moderate correlation (Larsen, Christensen, Nolan, & Sondergaard, 2004) between daily EE and

VO_2max, indicating that an individual who engages in a high amount of self-reported RPA does

not necessarily have a high aerobic capacity. This is particularly true as multiple factors

influence VO_2max, including biological, environmental, and the degree or extent of AE-based

training (Larsen & Sheel, 2015; Martinez-Vizcaino & Sanchez-Lopez, 2008), thus impacting the

ability of VO_2max to reflect an individual's RPA. For example, males and females differ in

aerobic capacity with females usually having a lower VO_2max and maximum power output

(PO_{max}) values compared to men (Cureton & Bishop, 1986). Thus, individuals may need to

engage in higher amounts of VPA specifically to improve aerobic fitness as adaptations occur at

higher PA intensities (CDC, 2019).
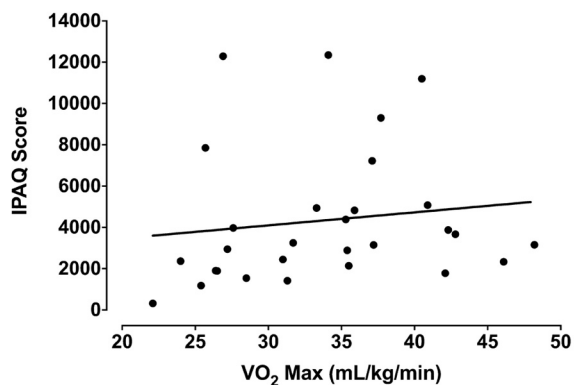
Figure 11. Relationship between IPAQ scores and VO_2max values. Slope of the line in scatterplot indicates line of best fit. This graph displays how the IPAQ has weak associations with aerobic fitness as individuals with low IPAQ scores show both low and high VO_2max scores (MacDonald, 2017). This suggests that VO_2max does not reflect an individual's level of aerobic activity.

2.5.2   Physical Activity and Corticospinal Excitability. Although there is limited

knowledge surrounding the mechanisms of the positive effects RPA has on brain structure and

function (Smith et al., 2014), there are a few studies indicating that individuals with higher levels

of PA, measured by the IPAQ, have increased CSE at rest. For instance, Cirillo and colleagues

(2009) classified RPA with the long-form of the IPAQ, where individuals self-report the

intensity and duration of their PA in five different domains (i.e., recreation/leisure-time,

household, sedentary, transportation, and job-related) over the past week. Individuals who had 4

VPA sessions lasting for 60- minutes each session, or 5 MPA sessions lasting for 90-minutes

each session were considered 'active', whereas those who had 3 or less sessions of walking for

20- minutes were considered 'less active' (but labelled as 'sedentary' in this particular study).

The authors stimulated individuals at rest with single pulse TMS (at 100, 110, 120, 130, and

140% of rMT) after paired associative stimulation (PAS), a technique which electrically

stimulates a peripheral nerve to induce neuroplastic changes within M1 via LTP-like

mechanisms. This concurrent application of PAS and TMS provides insight into the influence

different RPA levels have on brain plasticity. MEP amplitudes were recorded from the abductor

pollicis brevis (APB) and the first dorsal interosseous (FDI) hand muscles. CSE increased among

active individuals 5 and 30-minutes after PAS compared to sedentary individuals (see Figure 12).

Thus, when MEP amplitudes are higher, PAS was more effective at eliciting plasticity. When the

prior and post PAS MEP amplitudes were combined, the S-R curve was steeper by 35% among

the active individuals compared to sedentary individuals, indicating enhanced CSE and stronger

corticospinal connections among active individuals (see Figure 13). Thus, the greater facilitation

elicited by PAS among physically active individuals compared to sedentary individuals suggests

that only physically active individuals had an increased CSE response and short-term M1

plasticity. However, the effect RPA has on CSE remains to be clearly determined as there was considerable variability among the individuals classified as the same PA level (see Figure 14; Cirillo et al., 2009).
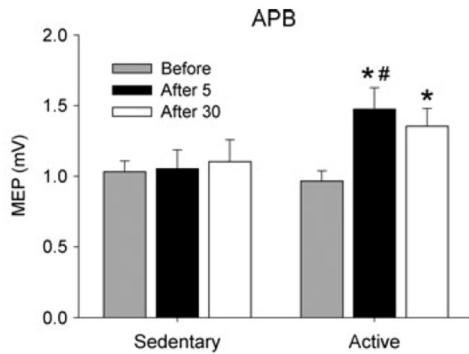
Figure 12. Mean motor evoked potential (MEP) amplitudes in sedentary and active subjects before, 5 minutes after (After 5) and 30 minutes after PAS (After 30). MEP amplitudes from the abductor pollicis brevis muscle increased from baseline among the active group 5 as well as 10 minutes after PAS, compared to the sedentary group. Higher bars indicate larger MEP amplitudes. $*p < .05$ compared with before PAS. $\#p < .05$ compared with the same time point in sedentary subjects. (Cirillo et al., 2009).
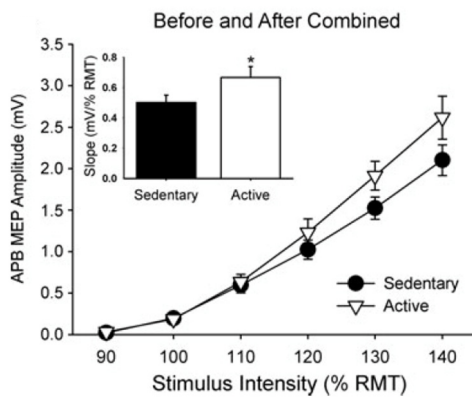
Figure 13. Motor evoked potential amplitude at each stimulus intensity. The slope of the curve has been calculated between 110 and 140% RMT and is shown in the inset of each group. The slope of the IO curve was significantly steeper in the active steeper in the active subjects (triangles) compared with the sedentary subjects (circles) when data were combined before and after PAS. $*p < .05$. (Cirillo et al., 2009).

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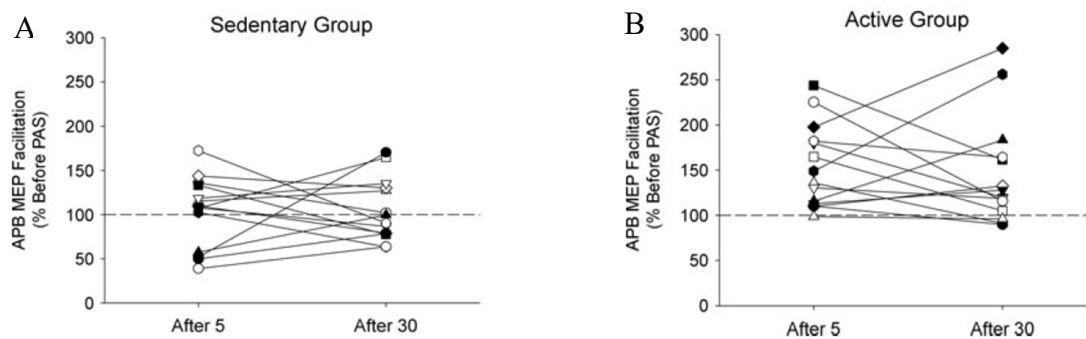
Figure 14. Individual subject variability in motor evoked potential (MEP) amplitude 5 mins and 10 mins after PAS. (A) the percentage change in MEP amplitude after PAS relative to before PAS in sedentary subjects and in (B) active subjects. The solid markers represent sedentary and the white markers represent active individuals (Cirillo et al., 2009).

Furthermore, it has been noted previously that chronic PA results in significant and distinct neuromuscular and physiological adaptations (Enoka, 1997). A specific adaptation noted in the nervous system is that chronic PA enhances neural drive to the muscular system affecting the discharge of motor-units, as well as the excitability of the motor neuron pool in the spinal cord (Enoka 1997). Thus, studies have investigated the differences between low and high PA levels on CSE and cortical inhibition after an acute bout of AE. A recent study investigated the influence a 20-minute bout of moderate intensity AE had on CSE after M1 stimulation among those with high and low PA levels (Lulic et al., 2017). The amount of PA was based on the IPAQ score. Twenty-eight participants were separated into two groups based on PA levels: 'high' (>3000 MET minutes per week) and 'low' (<3000 MET minutes per week). Moderate intensity AE was determined from HR_{max}, predicted from age: 220-age. The authors obtained MEPs from the FDI muscle using single pulse TMS. Following the 20-minute bout of AE at 60% of their age-predicted HR_{max}, CSE increased among individuals with higher PA levels compared to those

with lower PA levels (see Figure 15). Thus, the results revealed that more active individuals

(based on their IPAQ score) had a heightened response to AE, suggesting that higher RPA assists

with priming the brain for optimal responses to a bout of AE, and thus exercise- induced

plasticity, by creating an optimal neurochemical environment (discussed below in section 2.6.2).
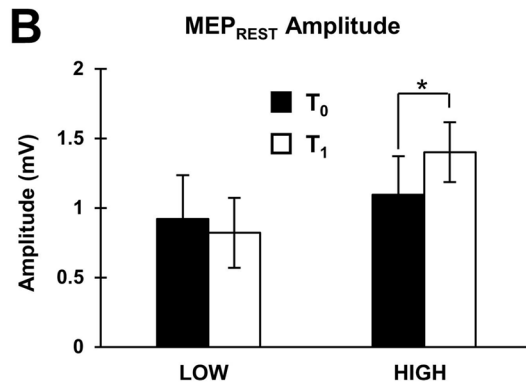
Figure 15. Comparing motor evoked potential (MEP) amplitude pre and post-exercise in high and low physically active individuals. Bar graph indicates the interaction between Time [pre-exercise (T0) vs post- exercise (T1)] x Group [HIGH vs LOW] for group-average MEP amplitude at resting motor threshold (MEPrest), with MEP amplitude on the y-axis and group on the x-axis. Cortical excitability increased after a 20-minute bout of moderate intensity AE among highly active individuals (HIGH; N= 13) compared to less active individuals (LOW; N = 14). * indicates $p < .05$. Error bars indicate standard error. (Lulic et al., 2017).

Although PA and AE have both shown promising evidence of inducing an environment

that assists with improving learning, memory and brain recovery in the adult brain, the high

degree of variability in CSE among individuals after AE that remains makes the understanding of

the role RPA has on brain function and short-term plasticity less clear (Cirillo et al., 2009).

Despite Lulic and colleagues showing higher CSE among highly active participants after

moderate intensity AE (supporting their hypothesis), some individuals showed opposite

responses or no response at all. For example, Lulic and colleagues reported ~31% of the

individuals in the highly active group did not increase in CSE after moderate intensity AE. While

many factors could have contributed to the variability within the PA groups, a main reason for this CSE variability within the same PA group was categorizing PA using the IPAQ as self-reports are highly inaccurate (discussed below). For instance, both low and moderately active were grouped into the same category (i.e, LOW), however, those who have very low amounts of PA (below 600 MET minutes per week on the IPAQ) may have vastly different CSE responses than a moderately active individual (above 600 but below 3000 MET minutes per week). Thus, another reason for this variability may be the brain-related adaptations that occur with different RPA intensities.

2.6   Individual variability in corticospinal excitability after aerobic exercise

 2.6.1   Issues with measuring PA via self-reported questionnaires. The IPAQ, a common subjective self-reported measure of PA (Sylvia, Bernstein, Hubbard, Keating, & Anderson, 2014), is prone to bias and thus potentially erroneous assessment of PA (e.g., response bias, memory bias, and social desirability biases; Brocklebank et al., 2015). In addition, the IPAQ standardizes the calculation of EE across individuals and types of activities, by multiplying the duration and frequency by a fixed MET minute for each category (walking, moderate, or high); thus, the intensity of the particular PA is not considered (Hagstromer et al., 2006). This may contribute to similarly classified individuals showing different cortical responses after moderate intensity AE as one may engage in high amounts of LPA while the other engages in low amounts of VPA.

Researchers have indicated that this inaccurate portrayal of RPA stems from the different interpretations of the PA intensity among individuals (Hillman et al., 2006). Hillman et al. (2006) used a self-reported questionnaire that had participants indicate frequency of sweating while engaged in PA on a scale of 0 (*no*) – 4 (*4 times per week*). However, this type of assessment of

PA results in the misreporting of PA as the degree of sweating varies among individuals, resulting in no indication of PA intensities.

Furthermore, based on the findings of previous studies, individuals report the intensity and duration of PA inaccurately causing the identified level of PA to be incorrect. For example, it has been shown that individuals tend to overreport the amount of VPA they engage in, and underreport the amount of MPA when compared to accelerometers - a more direct, objective, measure of PA. Previous work that generated Bland Altman plots between the IPAQ and the ActiCal, a triaxial accelerometer, indicated that the IPAQ underestimated EE for MPA (see Figure 16a) and overestimated EE for VPA compared to the ActiCal (see Figure 15b; Nang et al., 2011). For MPA, the mean difference of daily EE between the IPAQ and the ActiCal was 169kcal/day, whereas the mean difference between the IPAQ and the ActiCal was 139kcal/day for VPA. For VPA, agreement between the IPAQ and the ActiCal was similar when EE was below 400kcal per day, but reductions in agreement occurred as EE increased with greater instances of overestimations of EE (see Figure 16b). For example, the Canadian guidelines of 150 minutes of PA per week were being met by 52.5% of Canadian adults with self-reported PA levels, compared to only 15% when the measurement of PA was obtained via ActiCal accelerometers (Colley et al., 2011).
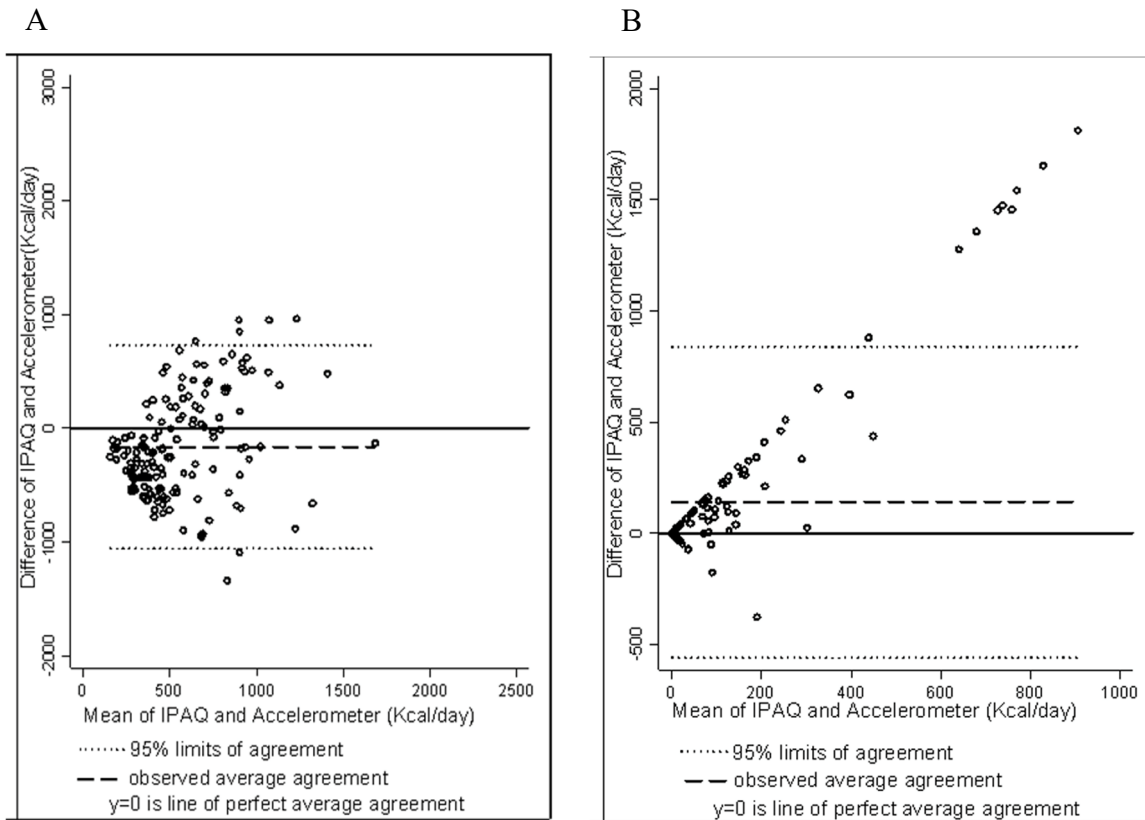
Figure 16. Degree of agreement of energy expenditure between the International Physical Activity Questionnaire (IPAQ) and ActiCal. (A) Bland Altman plots showing the agreement between the IPAQ and the ActiCal for moderate physical activity. The solid line indicates perfect mean difference in energy expenditure (kcal/day) between the two methods, the dotted line indicates 95% confidence intervals, and the dashed line indicates the mean agreement between the IPAQ and the accelerometer observed. The mean difference of daily EE between the IPAQ and the ActiCal was -169kcal/day. Thus, the IPAQ showed underestimations in kcal/day for moderate physical activity, compared to ActiCal accelerometer (Nang et al., 2011). (B) Bland Altman plots showing the agreement between the IPAQ and the ActiCal for vigorous physical activity. The solid line indicates perfect mean difference in energy expenditure (kcal/day) between the two methods, the dotted line indicates 95% confidence intervals, and the dashed line indicates the mean agreement between the IPAQ and the accelerometer observed. The mean difference between the IPAQ and the ActiCal was 139kcal/day. When the kcal/day was ~400, there was good agreement between the IPAQ and the accelerometer, however the IPAQ showed overestimations in kcal/day for vigorous physical activity levels, compared to the ActiCal accelerometer, above 400kcal/day (Nang et al., 2011).

Although the IPAQ enables computation of a weekly MET minute score providing a

subjective measure of RPA level, the issues noted above suggest it is not the ideal tool to assess

RPA. Similarly, aerobic fitness (assessed via VO$_2$max) is also not an ideal measure of an individual's RPA, as indicated above. Given the issues with these tools in assessing PA, this study investigated the role RPA levels have on CSE, quantifying RPA using activity counts per minute derived from accelerometry, a method thought to be a more accurate assessment of RPA (Colley et al., 2011).

2.6.2   *Physical Activity related brain adaptation.* Although the influence that RPA has on brain function is less clear (Cirillo et al., 2009), an individual's RPA pattern has been suggested to be associated with increased neuroplasticity (Lulic et al., 2017). These beneficial influences of PA on neuroplasticity are argued to be enhanced among those who engage in PA due to differential concentrations of certain neuromodulators, such as (1) Brain derived neurotrophic factor (BDNF; Knaepen, Goakint, Heyman, & Meeusen, 2010), and (2) lactate (Moscatelli et al., 2010).

BDNF is released in response to PA, and is important for the survival, and function of neurons, by promoting the specialization and growth of new neurons in the nervous system (Bathina & Das, 2015), facilitating synaptic plasticity (Knaepen et al., 2010). In animal research, serum BDNF (sBDNF), produced in peripheral blood cells, was shown to increase among the rats who consistently engaged in voluntary wheel-running for 7 days (Cotman & Berchtold, 2002). Similarly, Nofuji and colleagues (2012) investigated the difference in sBDNF concentration between active and sedentary healthy Japanese females, determined by duration of sports engaged in per week for at least 3 years. Those considered 'active' were engaged in chronic PA, playing sports 3 or more times per week for 3 or more years, whereas those who were 'sedentary' were not engaged in chronic PA for at least one year. An accelerometer was worn for a week prior to the AE sessions to ensure RPA levels were different between the two

groups of individuals. Since AE stimulates the release of BDNF, sBDNF concentrations collected at rest (before), as well as immediately, 30 minutes (P30), and 60 minutes (P60) after each AE session (low, moderate, and maximal intensity AE) on the cycle ergometer. Participants performed the GXT for the maximal intensity AE session on the first day of testing, lasting 15-20 minutes. The highest VO_2 in which an individual reached during the GXT (VO_{2peak}) was used to determine the percentage of VO_{2peak} for the low and moderate intensity AE sessions. Thus, the low intensity AE bout was 40% of VO_{2peak}, and the moderate intensity AE bout was 60% of VO_{2peak}. The low and moderate intensity AE bouts were 30-minutes in duration and were completed on either the second or third day of testing (counterbalanced between participants).

Changes in sBDNF were shown to alter based on the AE intensity and differed between active and sedentary individuals. Immediately after the GXT (see Figure 17a; Nofuji, Suwa, Sasaki, Ichimiya, Nishichi, & Kumagai, 2012), both active and sedentary individuals significantly increased in sBDNF; whereas sBDNF did not significantly increase after moderate (see Figure 17b) or low intensity AE (see Figure 17c). However, more physically active individuals showed reduced sBDNF levels below resting levels 30 minutes and 60 minutes after maximal AE as the uptake of sBDNF became more efficient, whereas sedentary individuals returned to baseline levels of sBDNF. Thus, sBDNF levels reduced faster 30 minutes after maximal exercise among individuals with more PA compared to sedentary individuals. In addition, the increased sBDNF has been associated with increased motor cortex excitability (Caumo et al., 2016). This may suggest that the higher concentrations of sBDNF immediately

after maximal AE among sedentary individuals indicate higher motor cortex excitability in comparison to those with more PA.
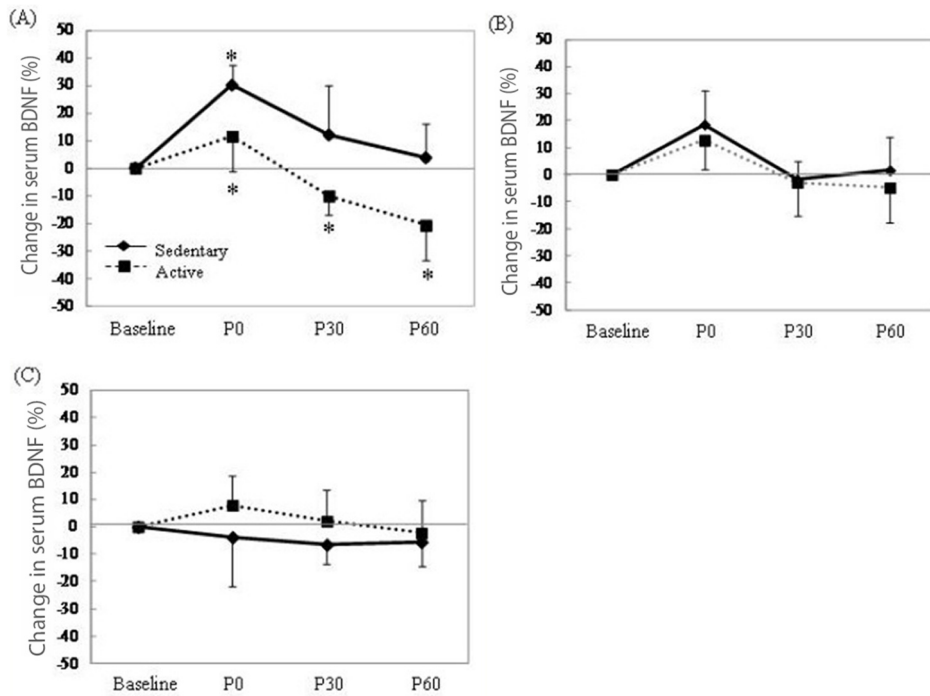
Figure 17. Relationship between change in serum BDNF (sBDNF) and physical activity levels at different aerobic exercise (AE) intensities. Line graphs indicate change in resting levels of sBDNF (baseline) immediately after (P0), 30 minutes after (P30), and 60 minutes after AE (P60) between sedentary and active individuals. Active individuals (>3 times a week playing sports) showed more efficient uptake and utilization of sBDNF at P30 and P60 time points only after (A) maximal AE ($p < .05$) compared to (B) moderate exercise intensity or (C) low exercise intensity AE. sBDNF increased immediately after maximal AE among both groups, however those more active reduced below baseline levels after AE. Error bars indicate standard deviation from the mean (mean ± SD). * Significant from baseline ($p < 0.05$). The changes in sBDNF responses for the groups were assessed by two-way repeated ANOVA. As an interaction and main effect of time were significant, one-way ANOVA followed by a Dunnett's post-hoc test was performed (Nofuji et al., 2012).

The effect of moderate intensity AE on sBDNF observed in this study was similar to Schmolesky and colleagues (2013), who showed a significant increase in sBDNF from baseline levels immediately after 20 minutes of moderate intensity AE, regardless of PA levels. However, there was no change in sBDNF concentration between active or sedentary individuals after the 30-

minute moderate intensity AE bout, as well as after the 30-minute low intensity AE bout. Similar to Schmolesky and colleagues (2013), it was shown that, regardless of PA levels, high intensity AE had greater increases in sBDNF from baseline than moderate intensity AE. This may indicate the enhanced utilization of circulating BDNF among those more active, compared to sedentary individuals, to promote muscle repair after maximal intensity AE (Nofuji et al., 2012). It was also confirmed that a dose-response relationship exists between AE and increased BDNF (Knaepen et al., 2010), which differs among those with more PA compared to sedentary individuals.

More specifically, the levels of sBDNF production increases with more activity, whereas levels of sBDNF production decreases with prolonged time spent sedentary (Swain et al., 2012). Further, lower sBDNF was shown among Japanese males who were more physically active (i.e., at least 16 hours per week of playing sports for more than 3 years; the 'trained' group) compared to a group of untrained Japanese males ('control'; Nofuji et al., 2008; see Figure 18). The total energy expenditure (TEE), movement-related EE (MEE), and walking count (WC) accumulated over the one week among the more active males was significantly higher than the control (referred to as 'sedentary' in the study) males (Nofuji et al., 2008). Using TEE and step count, measured by an accelerometer device, this study found that lower sBDNF among those with greater amounts of PA, specifically VPA, results in a more efficient uptake of BDNF and recovery of damaged tissue (Nofuji et al., 2008; see Figure 19). The authors suggested the lower sBDNF levels, on average, among physically active males was a result of the lower need for controlling energy balance or eating behaviour, due to the higher EE, as sBDNF is produced to increase EE, improving the metabolism of glucose as well as lipids. As this study was on Japanese males, the lower sBDNF levels may be due to the BDNF gene polymorphism which

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occurs in 50% of the population. This gene polymorphism alters intracellular trafficking and

reduces brain production of sBDNF during exercise by 25% (Shimizu et al., 2004). Although it

has not yet been determined whether sBDNF is related to increased CSE however, the

upregulation of sBDNF after AE contributes to motor learning and post-stroke rehabilitation by

facilitating neuroplasticity, neurogenesis, and neuroprotection (Mang et al., 2014).
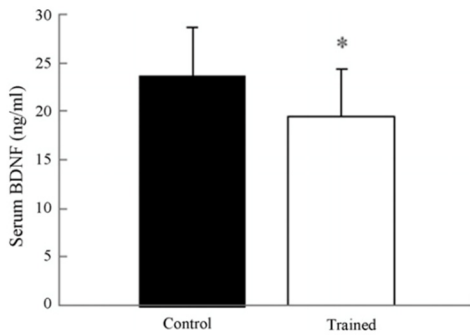
Figure 18. sBDNF comparison between individuals with higher PA to counterparts. Bar graphs show the sBDNF level in the control (n = 14) and the trained groups (n =12). Higher bars indicate higher sBDNF levels. Results reveal reduced levels of sBDNF among individuals with higher levels of habitual PA, according to the Lifecorder accelerometer. Data are expressed as the mean $\pm SD$. * p < .05 compared to control. (Nofuji et al., 2008).
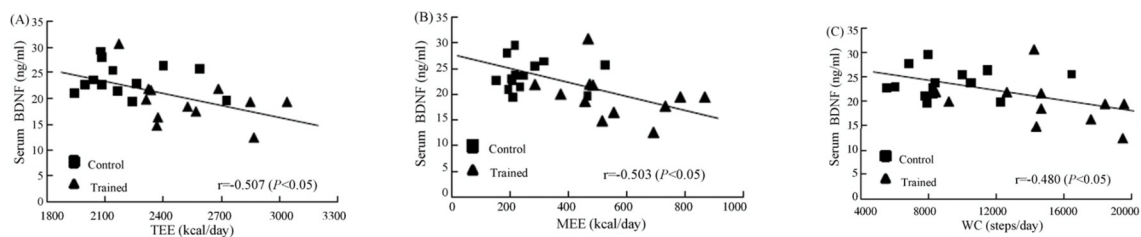
Figure 19. sBDNF relationships with EE. Relationship between the sBDNF level and (A) total energy expenditure (TEE), (B move-related energy expenditure (MEE), and (C) walking count (WC). Individuals in the control group (squares) had not participated in regular exercise for more than 1 year, while individuals in the trained group (triangles) were involved with PA. Results indicate a significant negative correlation between TEE, MEE, and WC and sBDNF, which reveals lower sBDNF levels among individuals with higher levels of habitual PA. (Nofuji et al., 2008).

Another neuromodulator that has been shown to be associated with neuroplasticity (Newman, Korol, & Gold, 2011), as well as CSE (Moscatelli et al., 2016), is blood lactate. Lactate is a by-product of glucose metabolism, the breakdown of glucose into energy anaerobically (without oxygen) within a muscle cell (Rogatzki, Ferguson, Goodwin, & Gladden, 2015), as well as in the brain (Riske, Thomas, Baker, & Dursun, 2017). Specifically, lactate has been found to enhance BDNF at rest (Schiffer et al., 2011), and is thus associated with mediating LTP-like plasticity (Singh et al., 2015). Lactate accumulates within the blood during AE, with higher lactate levels observed at higher intensities of AE (Moscatelli et al., 2016). Acute AE enhances the uptake of oxygen, lactate and glucose, all of which are important substrates for brain function. During maximal exercise, the brain extracts the accumulated lactate from the blood in a manner similar to glucose (Dalsgaard, 2006), suggesting a high sensitivity for lactate in the brain as muscles reach exhaustion. This response to lactate at the cortical level has been shown when individuals are at rest as well as when lactate is injected intravenously (Coco et al., 2010). Coco and colleagues (2010) stimulated the FDI muscle at a TMS intensity of 120% at rest, as well as immediately following, 5 minutes, and 10 minutes after a maximal GXT. Results indicated a negative relationship between rMT and blood lactate levels, whereby the percentage of the TMS stimulus intensity reduced immediately, 5 minutes, and 10 minutes following the AE bout, compared to before the AE bout. These results were associated with the increased blood lactate levels immediately, 5 minutes, and 10 minutes following maximal exertion, compared to pre-exercise levels (see Figure 20). The decrease in percent stimulus intensity following maximal AE indicates enhanced CSE, and the concurrent increase in blood lactate levels indicates blood lactate may facilitate the enhanced CSE (Coco et al., 2010).
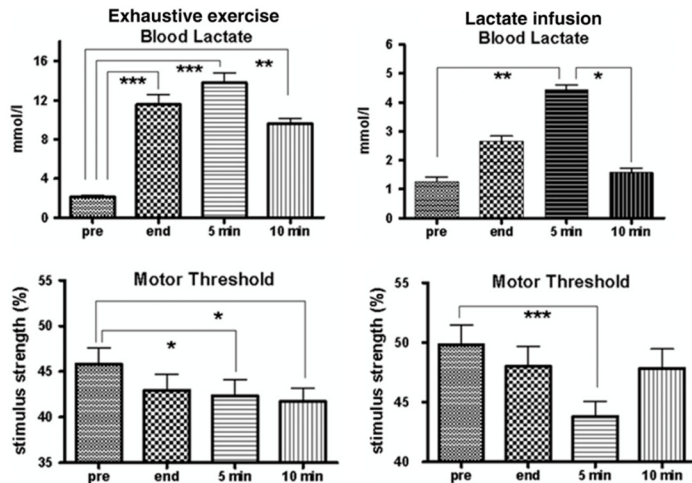
Figure 20. Comparing blood lactate concentrations and motor thresholds after maximal exertion and intravenously injected to baseline levels. Blood lactate concentrations, after a VO_{2max} test (top left), significantly increased from pre-exercise levels immediately after, as well as 5 and 10 minutes after exercise, compared to intravenous injections of lactate (top right) which only significantly increased from pre-injection levels 5-minutes after injection. Motor thresholds, after maximal VO_{2max} test (bottom left), significantly decreased 5 as well as 10 minutes after exercise, compared to intravaneous injections of lactate (bottom right) which only significantly decreased motor thresholds 5 minutes after injection. Bars represent standard deviation from the mean. *p < .05; **p < .01; *** p < .001. (Coco et al., 2010).

Moscatelli and colleagues (2016) further examined the relationship between time after a fatiguing hand gripping exercise and blood lactate levels among taekwondo athletes and non-athletes. The Lactate Pro©, a commonly used portable lactate analyzer (Bonaventura et al., 2015), was used to measure blood lactate immediately, 3 minutes, and 10 minutes after a fatiguing hand gripping exercise. First, lactate was shown to be associated with altering CSE levels as well as muscle fatigue, among both athletes and non-athletes (Moscatelli et al., 2016). A positive relationship between increased lactate levels and higher percent rMT (rMT%; discussed below), was shown immediately after a fatiguing hand gripping exercise (see Figure 21a). Said another way, as the concentration of blood lactate increased, so too did the rMT%, indicating a decrease in CSE, conflicting with the evidence shown by Coco and colleagues (2010) above. The results also demonstrated a significant, negative relationship between higher lactate levels and decreased

CSE, measured by the amplitude of the MEP in the FDS muscle, immediately after the fatiguing hand grip exercise (see Figure 21b; Moscatelli et al., 2016). These findings indicate that higher concentrations of blood lactate, as measured during the hand-grip exercise in millimole per litre by the Lactate Pro[©], were associated with a greater stimulus intensity required to elicit a motor response as well as lower MEP amplitudes, compared to those observed during lower concentrations of blood lactate. Thus, fatiguing exercises that result in higher lactate levels may be detrimental to CSE, reducing excitability. As noted above, these results were contrary to Coco and colleague's (2010) study, but may be the results of various factors, including the difference in the exercise performed (i.e., hand grip exercise vs a maximal GXT).

It should also be noted that Moscatelli et al. (2016) compared blood lactate concentrations between athletes and non-athletes. These results indicated significantly lower blood lactate accumulation immediately after a fatiguing hand-grip exercise among athletes (see Figure 22a). There was no significant change in rMT from baseline after the fatiguing exercise among nonathletes, whereas athletes showed a significant reduction in rMT from baseline immediately after the fatiguing exercise (see Figure 22b). This indicated that athletes had a more excitable brain, requiring less stimulus intensity to elicit a motor response. In regard to change in MEP amplitude from baseline levels, both nonathletes and athletes showed a significant decrease immediately after the fatiguing hand exercise, with nonathletes showing a greater reduction in MEP amplitude immediately after exercise, as well as after 3 minutes (see Figure 22c). Thus, athletes and non-athletes may differ in the degree to which the cortex is excitable after AE, as lactate does not accumulate in the brain as readily among athletes (Powers and Howley, 2008, pg. 277). The lower levels of blood lactate among athletes after the fatiguing hand grip exercise suggests that they have a higher lactate threshold, and greater excitability of the cortex,

compared to the non-athletes. Additionally, the differing blood lactate concentrations may be due in part by the increased blood flow at the working muscles as the capillary density at the muscle increases among athletes, allowing for greater oxygen extraction per liter of blood at a given submaximal AE intensity (higher a-$\bar{v}$ O_2 difference across muscles; Powers and Howley, 2008, pg. 277). In turn, lactate production reduces in the muscle, decreasing blood lactate levels, and delaying the onset of the accumulation of lactate within the blood among those more active (Powers and Howley, 2008, pg. 277). Since athletes may have a higher lactate threshold, this would result in a different response after the hand grip exercise as they would not be working at the same intensity as the non-athletes.

One reason underlying the increased blood lactate threshold among athletes is the increased perfusion to the brain that is associated with higher amounts and intensity of RPA compared to lower levels of perfusion observed with lower amounts and intensity of PA (Petriz et al., 2016). For instance, there is a relationship between lactate threshold and VO_{2max} (see Figure 23; Zoladz, Majerczak, & Grassi, 2016), whereby trained individuals reach their lactate thresholds at 65-80% of their VO_{2max} compared to untrained individuals who reach their lactate thresholds at 50-60% of VO_{2max} (Powers & Howley, 2008). Thus, as there are individual differences in the handling of lactate that relate to RPA levels, there is evidence to support the notion of an optimal AE intensity that would elicit an increase in brain excitability.
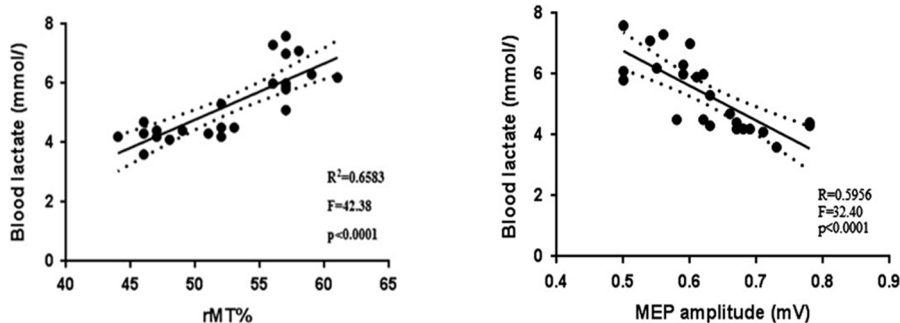
Figure 21. Blood lactate level relationship with MEP amplitude. A (left). The relationship between blood lactate concentration and the threshold for eliciting a motor response via TMS (rMT%) after a maximal exertion hand exercise. As lactate level in the blood increases, the threshold for eliciting a motor response increases, demonstrating a reduction in cortical excitability. B (right). The relationship between blood lactate concentration and the amplitude of the evoked motor response (MEP). Decreasing concentration of lactate results in a larger amplitude MEP, via rTMS over the FDS muscle, indicating greater cortical excitability and reinforcing the notion that high levels of lactate reduce cortical excitability (Moscatelli et al., 2016).
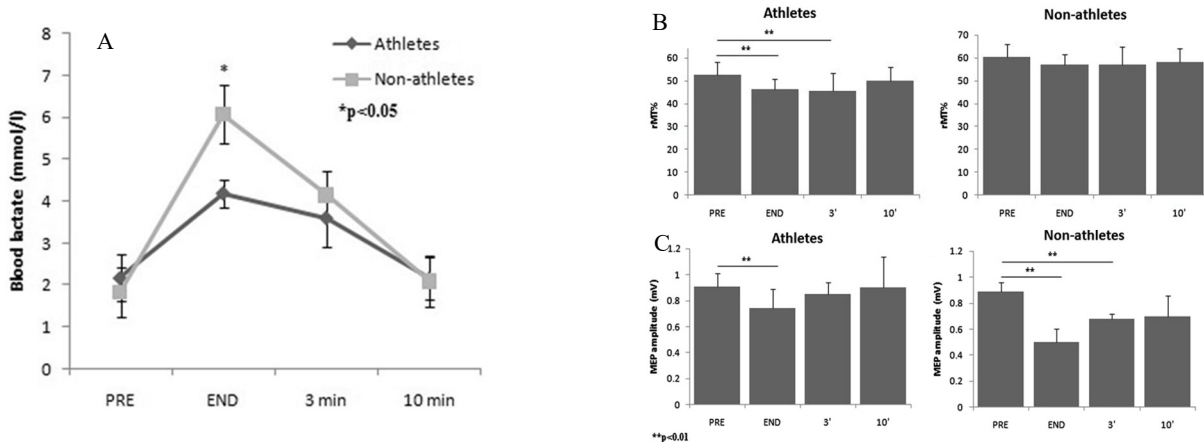
Figure 22. Comparison of blood lactate and MEP relationship between athletes and non-athletes. A. Line graph indicates changes in blood lactate levels at rest (PRE), at the end (END), 3 minutes post exercise (3 min), and 10 minutes post exercise (10 min). Taekwondo athletes showed lower blood lactate levels after fatiguing exercise (END) compared to non-athletes (p < .05). Error bars indicate standard deviation from the mean (Moscatelli et al., 2016). B. Compares rMT between athletes and non-athletes. Bar graph indicates the percentage resting motor threshold (rMT%) at rest (PRE), at the end (END), 3 minutes post exercise (3'), and 10 minutes post exercise (10') for athletes (A) and non-athletes (B), with higher bars indicating a higher rMT%. Athletes showed a significant decrease in rMT% at the end of exercise, as well as 3 minutes post-exercise, compared to at rest; whereas non-athletes showed no difference in rMT%. This indicates that CSE was higher after the fatiguing hand exercise among athletes whereas non-athletes had the same level of CSE. **indicates significant at the p < .01 level. C. Compares

MEP amplitude between athletes and non-athletes. Bar graphs indicate the MEP amplitude elicited at rest (PRE), at the end (END), 3 minutes after exercise (3'), and 10 minutes after exercise (10') for athletes (C) and non-athletes (D), where higher bars indicate higher MEP amplitude. Athletes and non-athletes showed a lower MEP amplitude at the end of the fatiguing hand exercise; however non-athletes also showed lower MEP amplitudes 3 minutes after exercise whereas athletes did not. (Moscatelli et al., 2016).
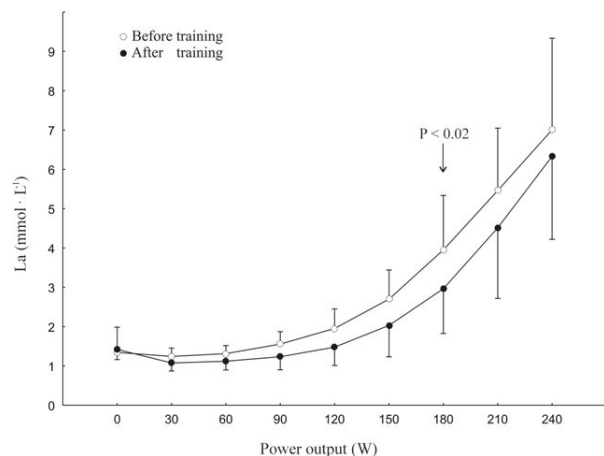
Figure 23. The relationship between plasma blood lactate concentration during an incremental exercise test before and after training. The plasma blood lactate concentration increased incrementally as the power output increased by 30W every 3 minutes. After training a shift in the curve to the right was found (solid dots), compared to before training (white dots). The difference before and after training was significant (p < .02) at 180W. Bars indicate standard deviation from the mean. (Zoladz et al., 2016).

With evidence of differential concentrations of blood lactate, as well as sBDNF, at a given intensity of AE between individuals who engage in more PA relative to those who are less active, there may be differential influences on CSE as well. A core component of this research was to objectively capture individual participants RPA behaviours in order to more accurately explore the relationship between a person's RPA behaviours and their response to AE as it relates to CSE.

2.7   Measuring physical activity objectively with accelerometers

Unlike self-reported measures that determine PA intensity using calculated MET minutes, such as the IPAQ, accelerometers determine PA intensity using activity count cutoffs

(discussed below). Uni-axial accelerometers (i.e., ActivPAL) record body accelerations, in G-forces (i.e., gravity units; John & Freedson, 2012) along the vertical axis only, while tri-axial accelerometers (i.e., ActiGraph) record body accelerations along three axes (i.e., vertical, horizontal, and perpendicular; Skender et al., 2016), corresponding to medial-lateral, vertical, and anterior-posterior planes of motion. Usually worn on the hip or ankle, accelerometers record the intensity, duration, and frequency of movement, providing a more precise and accurate measure of both the amount and intensity of PA (Sylvia et al., 2014).

According to previous literature, the ActivPal provides a valid assessment of postural allocations (i.e., sitting/lying, standing, and stepping; Barwais, Cuddihy, Rachele, & Washington, 2013), up/down transitions, as well as step count and steps per minute (i.e., cadence), thus accurately providing an assessment of SB among healthy younger adults (Grant, Dall, Mitchell, & Granat, 2008). Grant and colleagues (2008) also used a pedometer to determine the accuracy at each walking intensity which indicated a low absolute error (<1%) as well as a narrow limit of agreement from a Bland- Altman analysis. Thus, the current study used the ActivPAL to provide an assessment of each participants SB as a means to further characterize the study population.

Similar to uniaxial accelerometers, the measure of PA using triaxial accelerometers, such as the ActiGraph, has been shown to be a valid (Vanhelst et al., 2012) measure of PA in relation to VO_2 (Kelly, King, Goerlach, & Nimmo, 2013). Although no gold standard exists for measuring RPA due to the variety of means of measuring it (Diaz & Shimbo, 2014), as well as the different PA intensity cutoffs used across different accelerometers, activity counts derived from a triaxial accelerometer, measured per minute over a period of time, are normally used as a 'gold standard' for determining the equivalent PA intensity (Troiano et al., 2008; Troiano,

Gabriel, Welk, Owen, & Sternfeld, 2012). Different brands of accelerometers exist (e.g.,

ActiCal, ActiTrainer, ActiGraph, etc), each with their own activity count per minute cut points to

identify the duration spent in LPA, MPA, and VPA from the raw acceleration data. In order to

determine the MET values that correspond to these activity count cut points, Freedson and

colleagues (1998) measured VO_2 each minute, using open circuit spirometry, during 6 minutes of

slow walking (4.8km/h), fast walking (6.4km/h), and jogging (9.7km/h) on a treadmill. To

convert the measured VO_2 to METs, the steady state VO_2 was divided by 3.5mL/ kg /min (1

MET = 3.5mL/kg/min). Results showed a positive, incremental, relationship between the

increasing treadmill speed and VO_2 as well as the activity counts, with no differences between

males and females (Figure 24a and 24b, respectively). Thus, as speed of the treadmill increased,

VO_2 and activity counts incrementally increased.
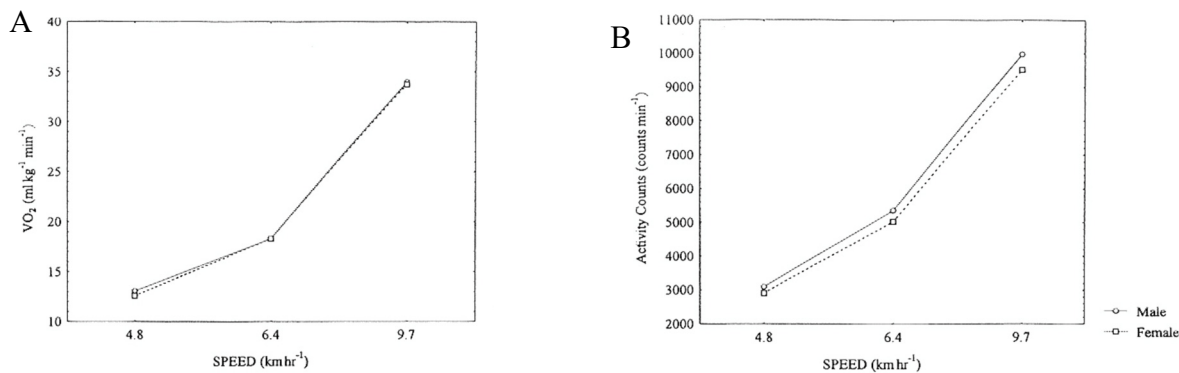
Figure 24. Gender comparison of metabolic and accelerometer relationship with different
treadmill speeds. (A) The line graph shows a positive, incremental, relationship between VO_2
and increasing treadmill speed, with no difference between genders. (B) The line graph shows a
positive, incremental, relationship between activity counts and increasing treadmill speed, with
no difference between genders. The solid line represents males, and the dotted line represents
females. (Freedson, Melanson, & Sirard, 1998)

Freedson and colleagues indicated that the MET values ranged from 3.7-9.7 METs for

the walking and jogging tasks (see Table 2). Further, the authors found a positive linear

relationship (r = .88) between these MET values and activity counts (see Figure 25). Thus, higher

MET values correspond to higher activity counts from the accelerometer. As the MET values

increase above 6 METs, the individual variability in activity counts increase, indicated by further

distances from the line of best fit. The derived regression equation to estimate METs from the

activity counts per minute (METs = 1.439008 +(0.000795 * counts per min), estimated activity

count ranges corresponding to MET intensity values commonly used in research were used (i.e.,

light = <2.99 METs, moderate = 3-5.99 METs, hard = 6- 8.99 METs, and very hard = >9 METs;

see Table 3 below). Thus, the activity count ranges can be converted to the corresponding PA

intensity as the MET upper and lower boundaries can be inserted into the regression equation.
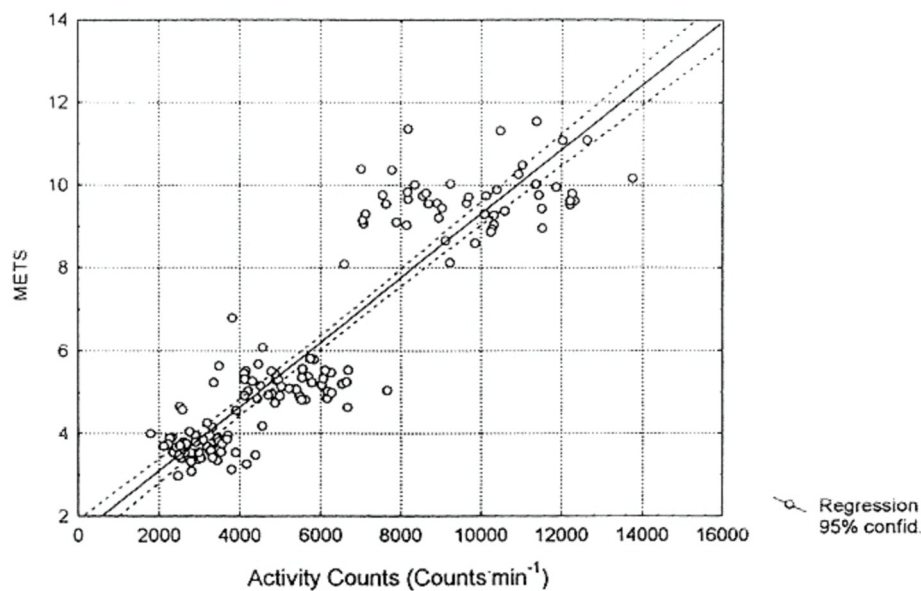
Figure 25. The relationship between activity counts and MET values. The scatterplot depicts the positive relationship between activity counts and MET values. Variability among individuals was low below 6 METs and increased above 6 METs, indicated by the distance from the solid line representing the line of best fit. The dotted lines represent the 95% confidence intervals. (Freedson et al., 1998)

Table 2. Corresponding activity counts to MET and VO₂ values at three different treadmill speeds.

Speed (km·h⁻¹)	V̇O₂ (mL·kg·min⁻¹)	METS	Activity counts (cnts·min⁻¹)
4.8	12.8 (1.2)	3.7 (0.3)	3003 (553)
6.4	18.3 (1.5)	5.2 (0.4)	5195 (943)
9.7	33.9 (2.6)	9.7 (0.7)	9749 (1768)

Table 3. MET and activity count ranges for each PA intensity

Activity Intensity	MET Range	Activity Counts (cnts·min⁻¹)
Light	<3.00	<1952
Moderate	3.00–5.99	1952–5724
Hard	6.00–8.99	5725–9498
Very hard	>8.99	>9498

With the use of the ActiGraph cut points from NHANES, we were able to obtain valid information regarding the individual's RPA behaviours, as well as accurately determine the duration spent in each intensity of PA.

2.8 Research Summary

It is evident from the previous research that when excitability in the brain is enhanced LTP is more likely to occur, and a single bout of AE can increase excitability in the brain, assisting in the learning of new cognitive or motor skills. However, there is considerable variability among these findings, possibly attributed to the differences in RPA levels among individuals. Further, evidence supports the notion that the intensity of PA an individual engages in regularly can result in different effects on the brain in general as well as alter the concentration of certain neuromodulatory agents that are linked to CSE and brain plasticity.

To address the variability in CSE responses after a single bout of AE, the objective of this research study was to determine the influence RPA behaviours have on facilitating CSE after a single bout of AE using accelerometers to measure RPA. We examined the relationship between RPA intensity and CSE at three different AE intensities (low, moderate, and high) to determine if there was a match between RPA intensity (i.e., percent wear time in LPA, MPA, and VPA) and AE intensity that leads to a change in CSE; a relationship that has not been investigated previously. It was hypothesized that the greatest increase in CSE would occur when higher percent wear times were accumulated in the same RPA intensity as the AE intensity engaged in, compared to when higher percent wear times were accumulated in an RPA intensity that was not the same as the AE intensity engaged in. To achieve this objective, each participant's RPA intensity was determined via accelerometry over a 9- day period preceding the experimental sessions. CSE was assessed via TMS before and immediately after a participant engaged in three separate AE bouts at the different intensities. This research aimed to improve knowledge related to the effects of AE on brain function and short-term plasticity as well as the individual characteristics, such as RPA, that influence this relationship, with the longer-term goal of improving individualized prescription of AE.

CHAPTER 3: METHODS

3.1 Participants

Twenty young adults (18-39 years old) participated in this study (13 females, 7 males; *M* = 25 years old). The sample was based on previous research that showed significant changes in CSE following a 20 minute bout of moderate intensity AE with samples sizes as small as fifteen (MacDonald et al., 2019). Participants were recruited from Dalhousie University as well as from the Halifax region via flyers (see Appendix 1) and word of mouth as we aimed to obtain a wide range of RPA behaviors. All participants were determined suitable for PA via the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+; Warburton, Jamnik, Brendin, & Gledhil, 2018; Appendix 3) and a Health History questionnaire (HHQ; see Appendix 6), as well as for TMS via a TMS screening form (see Appendix 4; Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Individuals who: take medications for anxiety or depression; are epileptic (or experienced a seizure); have suffered head trauma, a concussion, or loss of consciousness (including fainting); wear cochlear implants (i.e., reduced hearing) or a pacemaker were excluded. In addition, individuals with a respiratory disorder, hypertension or other cardiovascular diseases that would preclude participating in AE; a Body Mass Index $\geq$ 30kg/m2 and/or a waist circumference >102 cm for men and >88 for women; as well as smokers were excluded. In addition, if the individual's rMT (i.e., 'hotspot') could not be located during the first study session, the individual was excluded from the study. This study received approval from the Dalhousie University Health Sciences research ethics board.

3.2 Materials

3.2.1 Physical Activity Readiness Questionnaire (PAR-Q). The PAR-Q, created by the Canadian Society of Exercise Physiology, includes various questions on physical health. If the

individual answered 'yes' to any of the questions, they were unable to participate in the study (Warburton et al., 2014; see Appendix 3).

    3.2.2   Health History Questionnaire. The HHQ required the participant to indicate approximate weight and height, calculate BMI, and what exercise(s) he/she engages in (see Appendix 6). This was used to exclude participants with a BMI ≥30, as well as enter the weight (in pounds) into the analysis software program for the ActiGraph called ActiLife.

    3.2.3   TMS screening form. The screening form was provided to participants by e-mail prior to participating in order to identify those who may have contraindications to TMS that would preclude their participation. Similar to the PAR-Q, if the individual answered 'yes' to any of the questions, they were unable to participate in the study (Rossi et al., 2009; Appendix 4).

    3.2.4   Physical Activity and Sedentary Behaviour Questionnaire (PASB-Q). The PASB-Q is a self-reported questionnaire that determines whether the individual meets Canadian Physical Activity guidelines as well as provides total sedentary time (Fowles, O'Brien, Wojcik, d'Entremont, & Shields, 2017; see Appendix 8).

3.3   Overview of the Methodology

    This study consisted of wearing two accelerometers for 9 days and engaging in 3 AE testing sessions over a two- week period. AE sessions 1-3 were conducted on separate days with one day in between each. This 5-day period was required to ensure physiological responses were at baseline levels for each AE session and to reduce an order effect of the AE intensity performed, as well as fatigue in subsequent AE sessions.

    On Day 1, participants read the letter of information (Appendix 2) and completed an informed consent form (Appendix 5), the PAR-Q (Warburton et al., 2014; Appendix 3), the HHQ, and the TMS screening form (Rossi et al., 2009; Appendix 4) to verify eligibility for

participation. In addition, participants completed the PASBQ (Fowles et al., 2017; Appendix 8). The order in which the participant completed the questionnaires was random. The GXT was performed on a cycle ergometer to determine PO_{max}, and the associated HR_{max}. PO_{max} was used to determine AE intensity for the subsequent AE sessions (described below), and HR_{max} was used to determine if PO_{max} was reached. Additionally, in the first visit, the participants were introduced to the uniaxial accelerometer/inclinometer (i.e., the ActivPAL) and the triaxial accelerometer (i.e., the ActiGraph) that were worn for 9 days. The accelerometers were turned on and mounted to the hip (ActiGraph) and front right thigh (ActivPal; methods described below).

During the 9 days, participants were asked to keep a daily log, modified from O'Brien and Johns (2017), of the activities in which they engaged in, as well as accelerometer wear time, to ensure proper representation of RPA and to account for activities that the accelerometer may not record (i.e., cycling or swimming); see Appendix 9. Lastly, TMS was performed on the first day to ensure rMT could be obtained from the participant. The first AE session took ~1.5 hours to complete. After the initial 9 days of data collection using the accelerometers, the AE sessions took place at the Laboratory for Brain Function and Recovery. The AE sessions examined the effects of a single bout of AE on CSE. For each AE session, participants engaged in bouts of AE at low- (40% PO_{max}), moderate (60% PO_{max}) or high intensity (80% PO_{max}) on a cycle ergometer with TMS measures of CSE obtained before, and immediately after the AE bout (similar AE intensities to Smith et al., 2015; an outline of the AE protocol is described below). The order of AE intensity was randomly assigned to prevent an ordering effect of AE on the brain response. In addition, blood samples were collected using strips (similar to those for testing blood glucose) before and after AE to determine if blood lactate levels were correlated with changes in CSE

after AE (Moscatelli et al., 2016). Each AE session took approximately 1.5 hours to complete. Individuals were debriefed of the study's objectives and hypotheses on the final, third session.

3.4   Data Collection Protocol

3.4.1   Graded maximal exertion test. An upright stationary cycle ergometer (Ergoselect 200P, Ergoline, Bitz, Germany) was used for the GXT. Resistance for slower and faster pedaling rates were adjusted for within the ergometer by an electromagnetic braking force. The resistance (watts) was changed automatically by a software program, thus individuals kept a consistent PO. The cadence was kept within a pedaling rate between 60-70 rotations per minute (rpm) as the most efficient cycling cadence is between 60-80 rpm (Coast, Cox, & Welch, 1985). HR was measured via a wrist worn monitor (Mio global, 2014, Physical Enterprises Inc., USA). Each individual started with a 5- minute warm up on the ergometer at a workload of 40W. After 5- minutes, the PO increased incrementally each minute by 20 W until the point of exhaustion. Participants were asked to report their rating of perceived exertion (RPE) on the Borg scale (Borg, 1982; see Appendix 8) throughout the GXT. These RPE were also used to confirm whether the three AE sessions were in fact significantly different in intensity (i.e., low, moderate, and high). The rating scale was from 6-20, where 6 is no exertion and 20 is maximal exhaustion. Participants provided their RPE at the end of the warm-up phase and then every 2 minutes during the GXT. The participant was asked to notify the experimenter when they believed they had one-minute left before approaching exhaustion. Once the individual completed the GXT, a final RPE was provided, followed by a 3- minute cool down phase. The same workload was given during the cool down phase as the warm up phase to lower HR back to resting levels. Thus, criterion for when the GXT was complete were: (1) a Borg rating ≥ 17; (2) a HR ± 10 bpm of age-predicted HR_{max} using the following regression equation: $208 - (0.7 \times age)$ (Tanaka et al., 2018); or the test

takes ~8-12 minutes. The GXT was stopped if the participant experienced cardiac signs and symptoms that need attention or when the rpm of 60-70 was no longer maintained. Other indications for stopping exercise among low risk adults include (see Table 4):

Table 4. General indications for stopping an exercise test (Pescatello and American College of Sports, 2014)

General Indications for Stopping an Exercise Test in Low-Risk Adults
• Onset of angina or angina-like symptoms
• Shortness of breath, wheezing, leg cramps, or claudication
• Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
• Failure of HR to increase with increased exercise intensity
• Participant requests to stop
• Physical or verbal manifestations of severe fatigue
• Failure of the testing equipment

As HR fluctuates between days, as well as within the same day (Huber et al., 2013), AE intensity was determined from the PO_{max} (i.e., the wattage of the last full minute completed in the GXT) by multiplying PO_{max} by the following percentages (Pinot & Grappe, 2017): 40% for low intensity, 60% for moderate intensity, and 80% for high intensity. Keeping the work constant throughout each AE intensity, the duration of the AE bout was determined by the work-power relationship: Work = Power x Time (see Table 5 below)

Table 5. Deriving exercise intensity and duration for each bout of AE from PO$_{max}$ (Pinot & Grappe, 2017).

Exercise Intensity	Power Output	Time	Work
			If PO$_{max}$ = 210
Low Intensity	40% PO$_{masx}$	12 mins	W = P*T = (40% PO$_{max}$) x 12 = 1008
Moderate Intensity	60% PO$_{max}$	8 mins	W = P*T = (60% PO$_{max}$) x 8 = 1008
High Intensity	80% PO$_{max}$	6 mins	W = P*T = (80% PO$_{max}$) x 6 = 1008

3.4.2   Accelerometers. The ActiGraph GTX3, was used to assess RPA intensities and duration, and the ActivPal^{TM}, was used to assess SB. These accelerometers were worn over 9 days in total to obtain 7 valid days of data, including 5 weekdays and at least one day on the weekend. This was due to the omission of the first two days of accelerometer data as PA behaviours may change after the GXT leading to an inaccurate reflection of RPA (Beltz et al., 2016). The ActiGraph measures body movements in three planes: vertical (Y), anterior-posterior (Z), and lateral (X) (Skender et al., 2016); and provides the intensity and duration of PA via activity counts, which can estimate EE. As indicated previously, NHANES cut points (shown in Table 6 for LPA, MPA and VPA; Troiano et al., 2008) were used to identify the PA intensities in this study. In addition, the caloric MET values that relate to each PA intensity were derived from walking as well as jogging, on a treadmill (Freedson et al., 1998).

Table 6. ActiGraph activity counts per minute and corresponding MET value for each PA intensity.

PA Intensity	Activity Counts (Toriano et al., 2008)	MET value (Freedson et al., 1998)
Sedentary	<99 counts/min	<1.5
Low	100-2019 counts/min	<3
Moderate	2020 – 5998 counts/min	3-5.99
High	>5999 counts/min	>6

As described previously, the ActivPal[TM] measures body movements in the vertical plane, accurately measuring step count and cadence during walking, similar to a pedometer (Grant et al., 2008), as well as duration spent sitting/lying, standing and walking (i.e., postural allocations). The ActivPal[TM], which is 5.3 x 3.5 x .7 cm, was adhered to the front of the right thigh using Tegaderm (medical film; see Figure 26a) and the ActiGraph, which is 3.5 x 3.5 x 1 cm, was strapped around the waist with the device overlying the right hip (see Figure 26b).

Since the ActiGraph could be taken on and off, time when the accelerometer was not being worn (i.e., non-wear time), was identified based on published guidelines (Troiano et al., 2008). These guidelines define non-wear time as 60 or more consecutive minutes with no activity counts, with inclusion of 1-2 minutes of counts between 0 and 100. A valid duration of wear-time is 10 or more hours of wear time, on 4 or more valid days (Colley et al., 2011).

Figure 26. Accelerometer placements. A (left). ActivPal accelerometer taped to the front right thigh with TegeDerm. B (right). ActiGraph accelerometer will be worn on the hip joint.

3.4.3   TMS and muscle activity. For the TMS assessment participants sat comfortably in a reclining arm chair, with their head rested on the headrest and the right arm relaxed on a pillow in their lap. Muscle activity of the first dorsal interosseous (FDI) was collected using EMG during the AE session and TMS testing. An upper limb muscle was chosen owing to the interest in the generalized effects of AE on CSE. The EMG signal was acquired using self-adhering, non-invasive, electrodes (1 x 3 cm; Q-Trace Gold; Kendall-LTP, USA) in a bipolar configuration with a 1 cm inter-electrode distance, sampled at 1000Hz with a bandpass of 25-100 Hz (1902 and Power 1401; Cambridge Electronics Design, UK) and stored for offline analysis. Electrode placement was based on Seniam guidelines (European Commission, 1999). On the hand, one electrode was placed on the muscle belly of the FDI (1 finger width proximal to the 2nd metacarpal phalangeal (MCP) joint), and another on the first phalanx of the second digit. A third electrode was placed on the olecranon process to serve as a ground. The EMG signal was sampled at 1000Hz with a bandpass of 25-100Hz (1902 and Power 1401; Cambridge Electronics Design, UK) and stored for offline analysis. After participant preparation, rMT of the cortical representation of the FDI in M1 was determined by locating the motor 'hotspot', the region where a MEP peak-to-peak amplitude of at least 50μV is found on 5/10 trials. The rMT was found on the first visit to determine eligibility to participate, as well as on each session prior to AE as the hotspot and rMT may differ between days (Huber et al., 2013).

TMS was delivered via a figure eight coil (Magstem Company Ltd, 70mm Alpha Coil) which was connected to a Magstim BiStim^2 system (Magstim Company Ltd, UK). The Magstim BiStim^2 system had two Magstim 200^2 units which were joined through a connecting module. BrainSight neuronavigation (Rogue Research Inc., Montreal, CA) was used to guide the positioning and orientation of the coil over the target motor region. The neuronavigation system

combines the position of the TMS coil to a template MRI (MNI-152), a generalizable image of the brain created from an averaged anatomical MRI derived from 152 neurologically healthy individuals. The neuronavigation software was connected to a Polaris optical position sensor (Northern Digital Inc., Canada), which consisted of two infrared cameras, emitters, and associated electronics, to monitor and pick up trackers in the space in front of its cameras. The glasses worn by the participant, the TMS coil, and the pointer for co-registering the individual's head each had three spheres that reflected infrared light emitted by the Polaris sensor emitters (i.e., retro-reflective markers). These markers gave the Polaris optical position sensor information to calculate the position and orientation of the trackers (see Figure 27). Within the neuronavigation software, prior to each of the experimental sessions, five anatomical landmarks (nasion, tip of the nose, glabella, as well as right and left pre-auricular points) were digitized for each participant's head and co-registered to the template MRI.
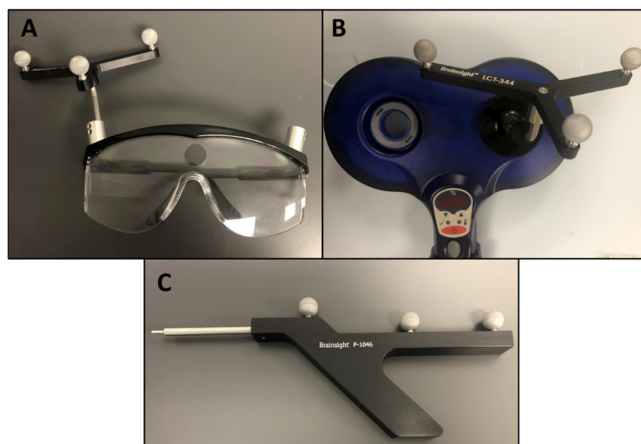
Figure 27. BrainSight trackers with retro-reflective markers (i.e., spheres) recognized by the Polaris sensor. (A) subject tracker, (B) coil tracker, and (C) pointer tool.

To localize the motor hotspot of the right FDI, a 5 × 5 cm grid (7.5 mm spacing) was placed overlying the cortical surface of the template brain with the mid-point (2, 2) centered on

the 'hand knob' of the left M1 (Kleim, Kleim, & Cramer, 2007; see Figure 28). With the handle of the TMS coil positioned 45 degrees to the mid-sagittal plane, the principal investigator stimulated various locations, starting at the mid-point, to determine the location that produced the highest MEP amplitude ($>50\mu V$) in the resting muscle for 5 out of the 10 stimulations at the lowest stimulator output intensity, assessed by MEP peak-to-peak amplitude.

After the rMT was determined, ten pulses at 120% rMT were delivered over the motor hotspot with a fixed inter-stimulus interval of 3 s between successive stimuli. With the exception of localizing the hotspot and determining rMT (i.e., when the stimulator was under manual control) the delivery of the TMS stimuli was controlled by a pre-programmed custom script using Signal software (Signal v 6.0, Cambridge Electronic Design Ltd., UK). This enabled external control of the stimulator via a hardware interface, including setting stimulus intensity and timing. Through the use of Signal, details related to the nature of the stimuli (i.e., intensity and type) were recorded along with the MEP, facilitating offline analysis.
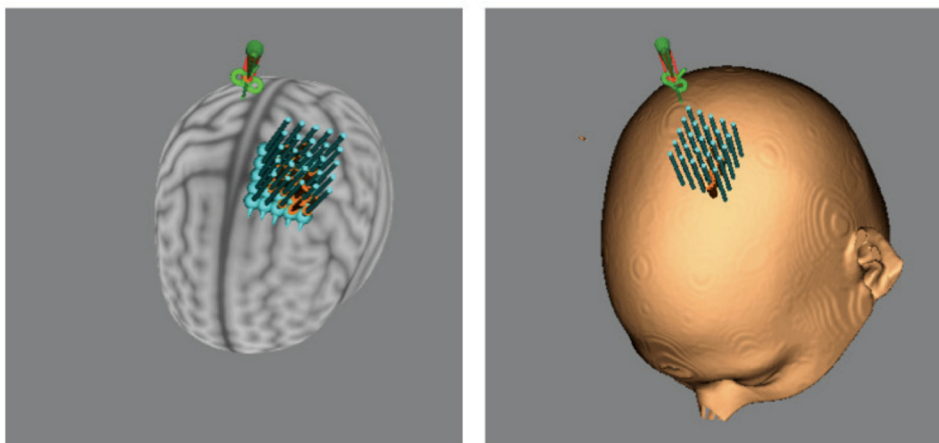
Figure 28. Stimulation target grid placement over the hand knob region of the left M1, shown in BrainSight. The reconstructed cortical surface is shown on the left, and the head shape is shown on the right.

3.4.4   Blood Lactate Measurements. The portable lactate analyzer used in this study was the *Lactate Scout* (EFK Diagnostics), which has similar reliability and accuracy in measuring blood lactate ion concentrations compared to the Lactate Pro[©] (Tanner, Fuller, & Ross, 2010). The materials required for measuring blood lactate included: alcohol wipes, blood lactate strips, *Lactate Scout* (see Figure 29), Surgilance[®] disposable lancets, biohazardous waste container, and Band-Aids[®]. Prior to the finger prick, the hand was sterilized and wiped with a Kleenex to remove excess alcohol as it would confound lactate readings. The skin was punctured with a small (23 gauge, 1.8 mm depth, Surgilance[®] grey) disposable lancet to obtain a blood sample (~2-3 drops). Subjects were provided with a Band-Aid if required. Blood lactate concentrations were digitally displayed in milimols per litre (mmol/L), which was immediately recorded by the *Lactate Scout* (EFK Diagnostics). The trained principal investigator conducted this procedure and a new lancet was used each time the finger was pricked. Blood lactate measurements were completed prior to the AE bout (resting value), during the last 2-minutes of the duration of the AE bout, as well as after the 5-minute cool down phase. Three separate finger pricks were done at each time point previously mentioned. Thus, in total, nine blood lactate measurements and 27 finger pricks were taken across the three AE sessions nine.

Figure 29. The Lactate Scout will be used to analyze the blood lactate levels, placing the lactate strip with the blood sample into the Lactate Scout which is then digitally read. The concentration of blood lactate will be digitally recorded in mmol/L.

3.4.5   Aerobic exercise sessions. The AE sessions occurred after the accelerometer data were collected, ~9 days after the first visit. After localizing the motor hotspot, as the location of the rMT may have changed from the previous measurement, single pulse TMS was applied at 120% rMT to obtain baseline CSE measures. Then, the participant exercised on the stationary ergometer at a low (40% PO$_{max}$), moderate (60% PO$_{max}$) or high intensity (80% PO$_{max}$), depending on the randomly assigned order. The random assignment was done using the random number generator function, RAND(), in Microsoft Excel, with the lowest number assigned to session 1, the highest to session 3, and the middle number to session 2 (see Appendix 10).

These AE intensities were derived from the PO$_{max}$ obtained at the end of the GXT and determined for each participant prior to the first AE session. The durations of AE were different with low intensity lasting 12 minutes, moderate intensity lasting 8 minutes, and high intensity lasting 6 minutes. Different durations of AE were employed to all for manipulation of AE intensity only while maintaining the same overall workload across the three intensities. Immediately following the AE bout, single pulse TMS was performed. In addition, each AE session was separated by at least one day, to reduce a physiological influence on the AE session, and the AE intensities were counterbalanced between participants (see Figure 30 below for full Methods) which was scheduled on Day 1.
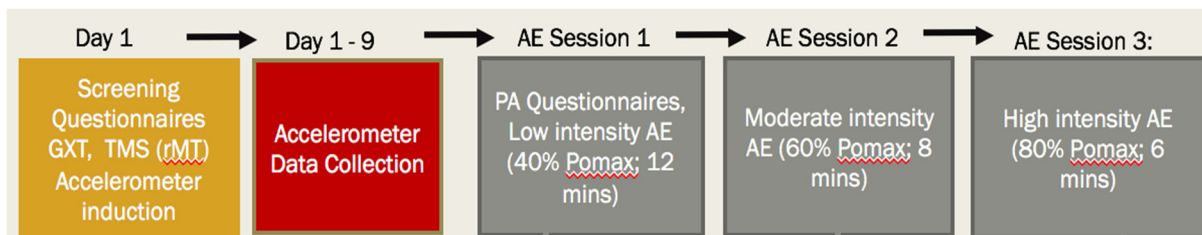
Figure 30. Full protocol. Lactate measurements were taken and single-pulse TMS was applied before and immediately after AE. AE intensity was randomly assigned to each AE session, with a minimal one day separating each AE session.

3.5   Data Analysis

3.5.1   Corticospinal Excitability Change Score. The MEP analysis was performed similar to past work in the Laboratory for Brain Recovery and Function (MacDonald et al., 2019). The Signal software program (Signal v 6.0, Cambridge Electronics Design, UK) recorded the stimulus intensity, and the EMG signal. The peak-to-peak amplitudes were calculated for each trial by averaging the 10 MEP amplitudes obtained at 120% rMT.

First, each frame was filtered within Signal using a 60 Hz notch filter to reduce power signal noise (Wang, Tang, & Bronlund, 2013). The custom script then isolated a 50 ms period in which the MEP should have occurred, thereby returning the peak-to-peak amplitude (i.e., the difference between the maximum and minimum values) in that specified time period, and the analysis period began 10 ms after the stimulus pulse was administered (1 second into each Signal from), since the typical latency of a MEP in the FDI after TMS is between 15 and 25 ms. Thus, the MEP amplitude occurring between 1.010 and 1.060 seconds was the interval of interest. The script included the MEP amplitude as well as the corresponding frame and was saved as a .txt file. These steps were repeated for each pre and post -exercise data file. After running the automated script the resulting MEPs were visually inspected (i.e., each frame that contained a single trial and thus one MEP) to ensure that (1) the timing of the stimuli and the responses were logical (e.g., the evoked response should appear after a the previously mentioned latency (depending on the participant's height); and (2) the peak-to-peak amplitude values obtained related to the evoked response (as opposed to an artefact). Then, the remaining MEPs were averaged for each stimulus intensity and used to generate a %CSE$_{change}$ from baseline. If a participant had lower than 3/10 MEPs at 120% rMT, the participant was excluded from further analysis. The EMG data were manually reviewed in order to determine if the amplitude values

calculated related to an actual MEP as opposed to signal noise (or artifacts). In addition, an automated script was run to calculate the root mean square (RMS) value of the EMG signal prior to the MEP amplitude to determine whether the baseline EMG exceeded one standard deviation of the average RMS, an indication of movement prior to the stimulus pulse (which would result in facilitation of the MEP). RMS values greater than one standard deviation from the average RMS would be flagged for manual inspection. If upon visual inspection the increased RMS amplitude was determined to be from movement prior to the stimulus pulse, the corresponding MEP was removed from the analysis. Therefore, in total each participant had 12 data files (2 pre and 2 post-exercise for low intensity AE; 2 pre and 2 post for moderate intensity AE; and 2 pre and 2 post for high intensity AE). These data files were exported to Microsoft Excel for further analysis.

To calculate the %CSE$_{change}$ from baseline the average MEP amplitude at 120% rMT post-exercise was divided by the average MEP amplitude at 120% rMT pre-exercise and then multiplying by 100. In Excel, the formula below was:

$$\%\text{CSEchange} = \left(\frac{Post\ average\ MEP\ amplitude}{Pre\ average\ MEP\ amplitude} \right) \times 100$$

This %CSE$_{change}$ from baseline (i.e., pre-exercise) calculation was repeated for each of the three AE sessions; thus, each participant had a %CSE$_{change}$ score for the single low, moderate and high intensity AE bout, whereby change scores over 100% indicated enhanced CSE and change scores below 100% indicated decreased CSE.

3.5.2 Accelerometer Physical Activity. To determine the participant's RPA behavior, intensity and duration from the accelerometer data over 7 valid days were analyzed. Thus, we omitted the first two days of wearing the accelerometer as PA behaviors after a GXT alter, with PA levels being reduced (as cited in Peluso & de Andrade, 2005). The accelerations recorded,

between 0.05-2.5 Gs (with a dynamic range of +/- 6 G's), were then converted into a digital signal by a 12-bit analog-to-digital converter at a sampling rate of 30Hz (ActiGraph, 2018). This digital signal was bandpass filtered between .25-2.5Hz and then extracted using a software program called ActiLife. ActiLife has built in algorithms for analyzing wear time, EE, cut points of PA intensity, MET rates, sedentary bouts, activity bout, inclinometer, sleep scoring, and heart rate. First, the raw activity counts across all 9 days were downloaded in 10 second 'epochs' (i.e., the summation of each sample collected every 10 seconds of wear time; Hwang et al., 2018; Gabriel et al., 2010). Ten second epoch length was used as previous research suggests shorter epoch lengths improve the precision and accuracy of the durations in specific RPA intensities (Matheson et al., 2016). The output within each epoch was provided in activity counts. Next, this file containing all activity counts per 10 second epoch was imported into ActiLife where wear time was validated, and the data were scored. For data validation, the criteria used was at least 10 hours of detected activity in a day. A tolerance of two minutes was built into the wear time validation where increases in activity during a sedentary bout (consecutive zeros) was still counted as an active bout if it was? under two minutes (i.e., spike tolerance). Data scoring was as follows: (1) the Freedson VM3 Combination (2011) formula was used to estimate EE as it uses all three axes in the estimation and combines the Freedson VM3 (2011) equation [VMCPM > 2453 counts per minute (CPM) then kcals/min = 0.001064 x VM + (0.087512*BM) – 5.500229] with the Williams Work-Energy (1998) equation [VMCPM < 2453 CPM then kcals/min = CPM x (0.0000191*BM)]; (2) the Adult Freedson (1998) equation was used to determine METs; and (3) the Torriano et al. (2008) cut points were used to determine LPA, MPA, and VPA. For the purpose of our study, we only used the output related to PA intensity rather than EE and MET values. The minutes accumulated in each PA intensity were averaged over the valid days for

each individual. However, since individuals had differing amount of valid days in the final analysis (range: 5-9 days), we normalized the minutes in each PA intensity to a percentage of wear time value (see formulas below). Thus, percent wear time per day was used to determine the relationship between LPA, MPA, and VPA and AE intensity on CSE.

$$\text{Percent wear time } = \left[\frac{\text{minutes of PA}}{\text{Average wear time}}\right] \times 100$$

$$\text{Average wear time per day} = \frac{\text{total wear time}}{\text{Number of valid days}}$$

Average wear time in LPA, MPA, and VPA were used to address the research question as the average wear time in total PA per day, or the vector magnitude (i.e., the square of the sum of all the activity counts per minute across all three axes) reflect RPA in general when collapsed across all RPA intensities and not each RPA intensity independently. The derived PA intensity durations from the vector magnitude is suggested to be less accurate, and lower in classification agreement, compared to the intensity durations from the vertical axis (McGarty, Penpraze, & Melville, 2016). The percent wear time per day in MVPA was found by adding the percent wear time per day in MPA and VPA together. This measure was used to determine whether an individual accumulated 150 minutes per week of MVPA (CSEP, 2018).

The raw data from the ActivPal[TM] was sampled at 10 Hz (Dowd, Harrington, Bourke, Nelson, & Donelley, 2012) and the duration of time spent stepping, standing, as well as sitting/lying were extracted using custom designed software that can be downloaded into easy-to-interpret graphs and spreadsheet (PAL Technologies, 2018). This information included daily summaries, hourly summaries per day, as well as the individual's PA behaviour every 15 seconds of wear time. If the individual was still active after midnight, the total amount of steps prior to the end of the active period (i.e., when sleeping) was subtracted from the current day and added to the steps taken on the previous day. These calculated steps per day, using only the valid

days, were averaged to obtain the average steps per day value (see below for calculation used). Further, the duration of sleep was subtracted from the calculated sitting/lying down time from the ActivPAL raw output to obtain the 'awake sedentary time'. These durations were averaged over the valid days for each individual and then normalized. To normalize the PA across participants' wear time for each PA measure were divided by the average minutes the accelerometer was worn for per day and then multiplied by 100 to create a percent wear time value (see above for calculation used).

$$\text{Average steps per day} = \frac{\text{Sum of steps per day}}{\text{Number of valid days}}$$

3.5.4   Statistical Analyses. All statistical analyses were performed using the statistical program for social science (SPSS) software (IBM SPSS 25, 2018). First, independent t-tests were performed between the RPE scores for each AE intensity session. This was done to determine if the AE sessions significantly differed from each other based on intensity. Secondly, the Shapiro-Wilk normality test was performed on the %CSE$_{change}$ scores for each AE intensity prior to the Pearson bivariate correlation test to determine whether the scores within each AE intensity session have a normal distribution. The null hypothesis tested states the scores within each AE intensity are normally distributed and was accepted if statistical significance (p) was below .05.

Pearson bivariate correlations were performed for each RPA intensity (percent wear time in LPA, MPA, and VPA) and the %CSE$_{change}$ after each AE bout (low, moderate, and high). This analysis allowed us to address our research question of whether a significant relationship existed between the %CSE$_{change}$ after the AE bout and the percent wear time in the matched RPA intensity.

Chapter 4: RESULTS

Out of the 20 participants tested, three were excluded: one participant was excluded for having a BMI that exceeded the study criteria and two participants did not have the required number of MEP's (one for the high intensity and one for the moderate intensity AE session). Thus, seventeen healthy young adults (n = 11 females, n = 6 males; M = 25.26 years old, SD = 3.91 years old) were included in the final analysis. All individuals had a BMI below 30 (M = 23.41; SD = 2.87), and the average weight and height of the participants was 67.02kg (SD = 12.47) and 1.69m (SD = .08) respectively. All participants successfully completed the GXT, reaching their PO_{max} (M = 188.42W; SD = 62.29) as well as reporting a final RPE above 17 on the Borg scale (see Table 7). Results related to the measurement of blood lactate levels were not included as our analysis revealed substantial deviation from published, normative values (detailed in section 5.3 below).

Table 7. GXT summary results

Participant #	Gender	Age	Weight (kg)	Height (m)	BMI (kg/m^2)	PO_{max} (W)	HR_{max}	Age predicted max HR_{max}	Max RPE	Plateau achieved?
1	Male	25	90.90273407	1.8	28.08	180	175	190.5	18	Yes
2	Female	32	53.44281619	1.6	20.89	160	174	185.6	20	Yes
3	Male	20	86.62131519	1.75	28.23	260	190	194	19	Yes
5	Female	24	56.93907519	1.56	23.42	100	174	191.2	18	Yes
6	Male	23	73.46938776	1.8	22.61	240	180	191.9	20	Yes
7	Male	30	60.93479976	1.69	21.36	240	184	187	19	Yes
8	Female	28	74.82993197	1.78	23.7	120	141	188.4	18	Yes
9	Female	22	52.15419501	1.6	20.39	160	172	192.6	17	Yes
10	Female	23	54.42176871	1.66	19.68	160	172	191.9	20	Yes
11	Female	20	65.75963719	1.6	25.71	140	172	194	17	Yes
12	Female	26	54.42176871	1.62	20.62	100	113	191.9	13	No
13	Female	25	65.75963719	1.61	25.22	160	179	189.8	18	Yes
14	Male	25	79.36507937	1.8	24.43	240	187	190.5	20	Yes
15	Male	22	74.82993197	1.7	25.86	280	187	190.5	18	Yes
16	Female	32	61.2244898	1.68	21.81	200	170	192.6	20	Yes
18	Female	21	54.42176871	1.64	20.11	160	173	185.6	18	Yes
19	Female	26	79.8185941	1.68	28.4	160	180	193.3	19	Yes
20	Male	25	90.90273407	1.8	28.08	160	172	189.8	18	Yes

Note. The age predicted HR_{max} was found using the equation from Tanaka, Monahan, and Seals (2001): Age predicted HR_{max} = 208-(0.7*Age)

4.1   Descriptive measures

4.1.1   Regular Physical Activity Behaviour. From the 7 days of wear time, the average minutes per day in the different postural allocations (sitting/lying, standing, and stepping), SB, LPA, MPA, VPA, and MVPA were calculated from the ActivPAL and ActiGraph data (see Table 8). As some participants had more than 5 valid days of wear time (see Table 8 final column), leading to the accumulation of more body accelerations and thus longer time spent in each RPA intensity, the average minutes per day were normalized into percent wear time per day (see Table 9 and Figure 31a for visualization of the ActivPAL data for each participant, as well as Figure 31b for visualization of the ActiGraph data for each participant).

Based on the average time spent in MVPA as determined from the ActiGraph data, all participants were found to meet the recommended guidelines except for one (indicated by the red bar in Figure 32a). The participant who did not meet recommended guidelines (CSEP, 2018) had an average MVPA of 29.27 minutes per day, whereas the other participants had an average MVPA >30 minutes per day (range 33.57 - 79.81 minutes). The self- reported scores from the PASBQ for each participant, along with the average PA per week from the ActiGraph is reported in Table 10 for direct comparison. Average steps per day ranged from 4862 (which coincidentally was the same participant who did not meet the CSEP recommended guidelines) to 18264 (see Figure 32b), with the average steps per day of XX across the sample. As indicated in the methods, the ActiGraph average percent wear time per day values for SB, LPA, MPA, and VPA were multiplied by 7 to obtain the average percent wear time per week.
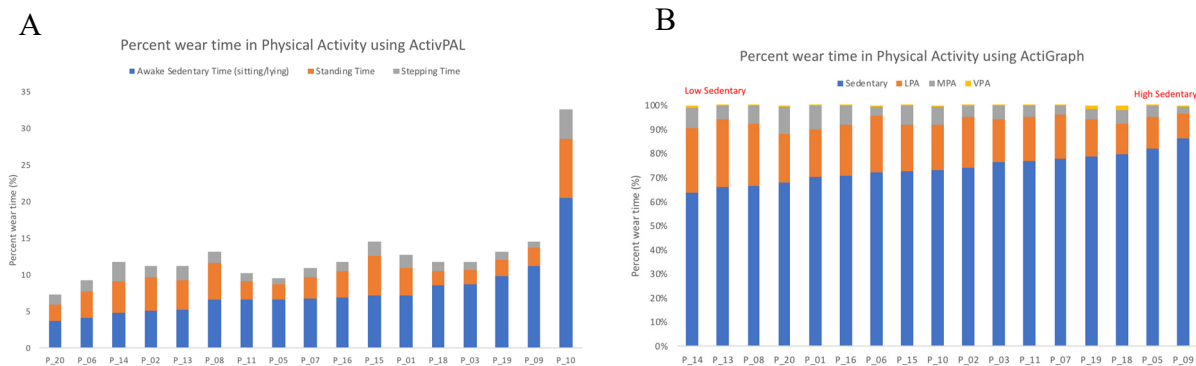
Figure 31. ActivPAL and ActiGraph normalized data. (A) The stacked bar graphs are ordered from low awake sedentary time (far left), to high awake sedentary time (far right). The more awake sedentary time, the less stepping time (and vice versa). Blue represents the normalized awake sedentary time, orange represents normalized standing time, and grey represents normalized stepping time. (B) The stacked bar graphs are ordered from low sedentary time (far left), to high sedentary time (far right). The more sedentary time, the less LPA and MVPA. Blue represents the percent wear time spent sedentary, orange represents percent wear time in LPA, and grey represents the percent time in MVPA.
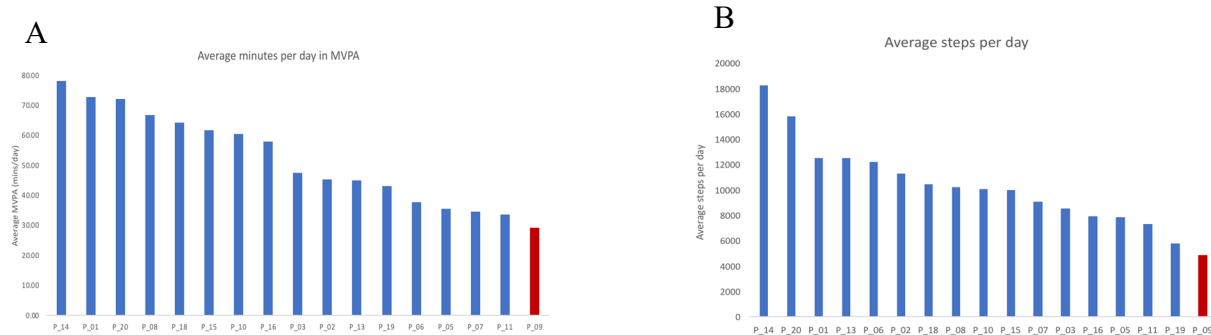
Figure 32. Average MVPA minutes per day and steps per week for each participant. (A) The bar graph depicts the average minutes per day of MVPA in order from highest (far left) to lowest (far right) MVPA. The red bar represents the participant who did not meet Canada's PA guidelines. (B) The bar graph depicts the average steps per day in ordered from the most steps per day (far left) to the least steps per day (far right). The red bar in each panel represents the participant that did not meet Canada's PA guidelines (i.e., below 150 MVPA per week).

Table 8. Raw accelerometer data from the ActivPAL and the ActiGraph for each participant.

	ActivPal (mins/day)				ActiGraph (mins/day)						
Participant	Awake Sedentary Time	Average steps	Standing Time	Stepping Time	Sedentary time	LPA	MPA	VPA	Total MVPA	Average MVPA	Valid Days
1	625.30	12577.33	321.40	148.80	510.50	144.25	72.33	0.31	72.64	72.64	6
2	443.60	11314.67	389.20	139.20	683.89	195.17	43.08	2.17	45.25	45.25	6
3	754.60	8537.00	167.00	99.10	641.08	149.64	46.72	0.83	47.56	47.56	6
5	766.80	7910.75	241.28	94.50	631.02	204.12	34.10	3.67	37.76	35.53	6
6	417.86	12242.86	360.00	162.77	686.67	158.22	32.75	1.81	34.56	37.76	7
7	588.70	9115.33	251.80	104.60	594.33	231.30	66.23	0.43	66.67	34.56	6
8	570.90	10251.00	435.00	136.40	721.87	85.63	25.77	3.50	29.27	66.67	5
9	808.92	4862.40	178.20	60.48	549.72	141.11	57.44	2.94	60.39	29.27	5
10	589.80	10062.00	234.30	113.70	567.13	135.07	31.80	1.77	33.57	60.39	6
11	574.00	7325.67	218.10	97.00	546.10	232.50	44.80	0.20	45.00	33.57	5
13	450.60	12561.00	347.90	164.40	544.67	228.58	69.11	9.14	78.25	45.00	5
14	422.10	18264.67	362.30	235.00	575.60	154.87	61.40	0.30	61.70	78.25	6
15	515.64	10030.40	396.12	131.52	511.72	151.83	56.53	1.44	57.97	61.70	5
16	594.60	7972.33	313.30	106.30	669.58	105.31	48.44	15.89	64.33	57.97	6
18	739.80	10506.67	168.40	114.40	416.32	121.72	68.27	3.95	72.22	64.33	6
19	710.40	5819	159.30	75.90	510.50	144.25	72.33	0.31	72.64	43.05	6
20	430.95	15802.75	254.10	166.95	683.89	195.17	43.08	2.17	45.25	72.22	5

Table 9. Normalized percent wear time per day for each RPA measures

	ActivPAL			ActiGraph				
Participant	Awake Sedentary	Stepping time	Standing Time	Sedentary	LPA	MPA	VPA	MVPA
1	7.24	1.72	3.72	70.18	19.83	9.94	0.04	9.99
2	5.13	1.61	4.50	73.99	21.11	4.66	0.23	4.89
3	8.73	1.15	1.93	76.48	17.85	5.57	0.09	5.67
5	6.66	0.82	2.09	82.01	13.34	4.54	0.11	4.65
6	4.15	1.61	3.57	72.29	23.38	3.90	0.42	4.33
7	6.81	1.21	2.91	78.08	17.99	3.72	0.20	3.93
8	6.61	1.58	5.03	66.61	25.92	7.42	0.05	7.47
9	11.24	0.84	2.48	86.27	10.23	3.08	0.42	3.49
10	20.48	3.95	8.14	73.18	18.78	7.65	0.39	8.04
11	6.64	1.12	2.52	77.08	18.35	4.32	0.24	4.56
13	5.22	1.90	4.03	66.31	28.23	5.44	0.02	5.46
14	4.89	2.72	4.19	63.96	26.84	8.12	1.07	9.19
15	7.16	1.83	5.50	72.66	19.55	7.75	0.04	7.79
16	6.88	1.23	3.63	70.92	21.04	7.83	0.20	8.03
18	8.56	1.32	1.95	79.79	12.55	5.77	1.89	7.66
19	9.87	1.05	2.22	78.91	15.48	4.40	1.22	5.62
20	3.74	1.45	2.21	68.22	19.94	11.19	0.65	11.83

Table 10. Self-reported questionnaire

| | Self- Reported Measure | | | | Objective Measure | | | |
| | PASBQ (mins/week) | | | | ActiGraph (mins/week) | | | |
Participant	Sedentary	LPA	MPA	VPA	Sedentary	LPA	MPA	VPA
1	2940	540	80	40	3573.50	1009.75	506.33	2.14
2	2940	0	170	135	4787.22	1366.17	301.58	15.17
3	2520	0	180	312	4487.58	1047.47	327.06	5.83
5	2520	100	45	0	4387.44	714.00	242.86	5.83
6	2520	175	120	180	4417.17	1428.83	238.67	25.67
7	4200	0	60	500	4806.67	1107.56	229.25	12.64
8	3360	110	160	30	4160.33	1619.10	463.63	3.03
9	2940	20	100	30	5053.07	599.43	180.37	24.50
10	2100	24	150	150	3848.06	987.78	402.11	20.61
11	2100	1200	600	720	3969.93	945.47	222.60	12.37
13	2520	420	180	30	3822.70	1627.50	313.60	1.40
14	2520	115	75	225	3812.67	1600.08	483.78	63.97
15	4200	160	60	120	4029.20	1084.07	429.80	2.10
16	1260	120	30	10	3582.06	1062.83	395.69	10.11
18	2520	0	360	0	4687.08	737.14	339.11	111.22
19	2100	120	120	90	4234.81	830.67	236.06	65.33
20	2100	325	335	640	2914.22	852.02	477.87	27.65

4.2   Influence of Physical Activity on Cortical Excitability.

4.2.1   Comparing RPE scores between AE sessions. On average, participants reported the three intensities of AE as having different RPE scores. Based on the Borg scale values, the high intensity AE bout was reported as 'very hard' ($M = 17$, $SD = 1.82$), the moderate intensity AE bout as 'somewhat hard' ($M = 13.47$, $SD = 2.06$), and the low intensity AE bout as 'very light' ($M = 9.68$, $SD = 2.08$) (see Figure 33). Statistical analysis showed that the RPE for the high intensity AE session was significantly higher compared to the moderate intensity AE session [$t(36) = 5.57$, $p < .001$], as well as the low intensity AE session, [$t(36) = 11.51$, $p < .001$]. Additionally, the average RPE for the moderate intensity AE session was significantly higher compared to the low intensity AE session, [$t(36) = 5.63$, $p < .001$].
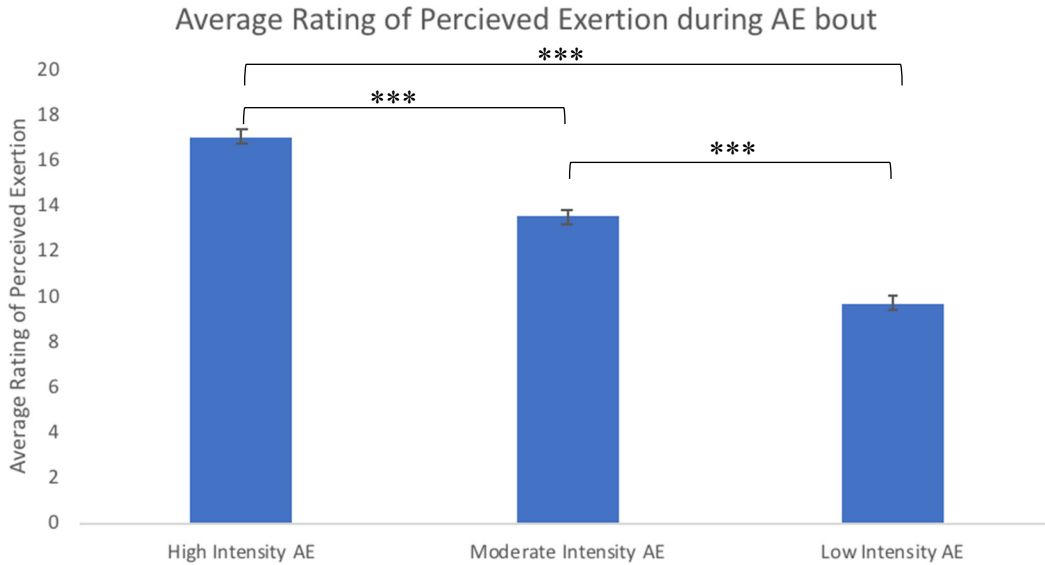
Figure 33. Comparison between RPE scores of each AE session. The bar graph depicts significant differences between average RPE scores from each AE intensity bout. *** indicates a significant difference (p < .001). The error bars represent SEM.

4.2.2   Normalizing distributions. The Shapiro-Wilk normality test revealed the distribution of %CSE$_{change}$ scores were not normally distributed for the high [D(17) = .21, p = .01], MI [D(17) = .22, p = .004] and low [D(17) = .20, p = .05] intensity AE sessions. Using the square root function in Microsoft Excel, the values were transformed to avoid Type 1 error (Field, 2013).

4.2.3   Correlations between RPA intensities and %CSE$_{change}$. Pearson bivariate correlations were performed in SPSS between each RPA intensity and the corresponding %CSE$_{change}$. There was a significant, positive, relationship between percent wear time in VPA and the %CSE$_{change}$ after high intensity AE (r = .52, p = .02; see Figure 34a). A weak, positive relationship between the percent wear time per day in MPA and the %CSE$_{change}$ after moderate intensity AE (r = .26, p = .30; see Figure 34b) was observed, with a similar relationship observed between the percent wear time in LPA and the %CSE$_{change}$ after low intensity AE (r = .15, p = .54; see Figure 34c), were not significant.
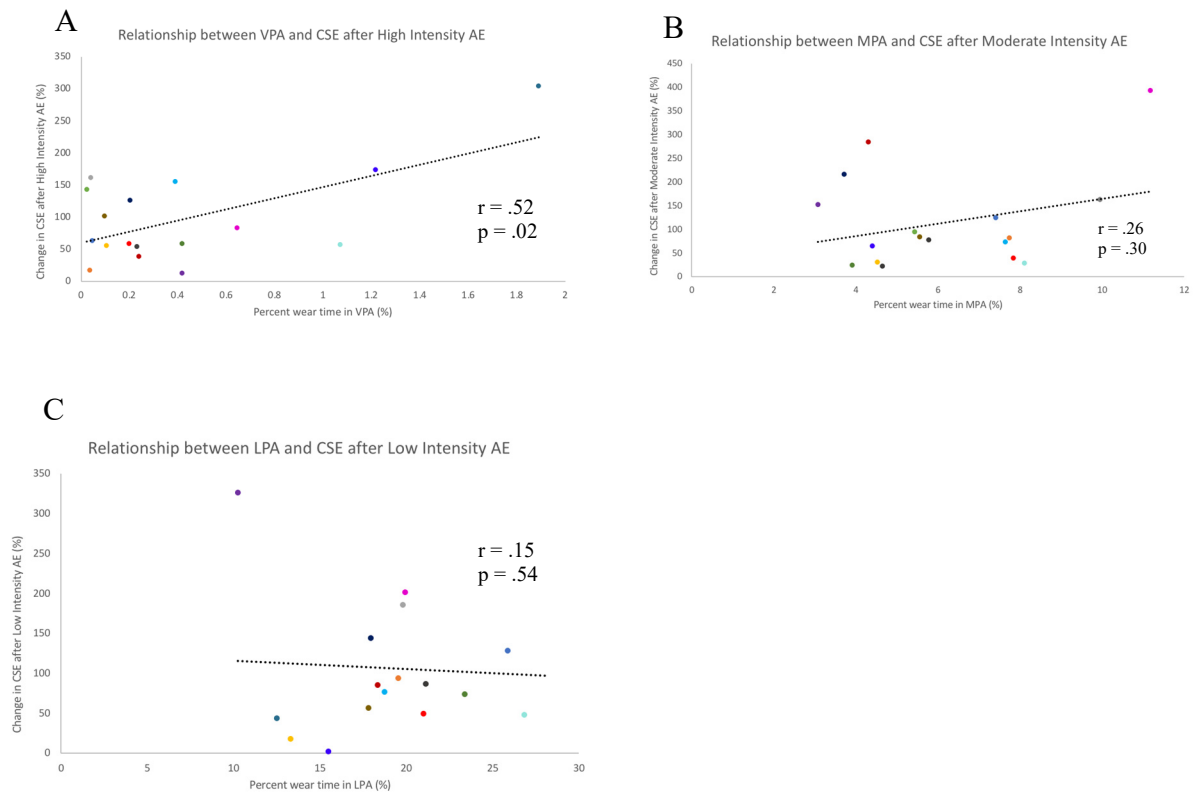
Figure 34. Relationships between RPA and %CSE_change after each AE session. (A) The scatterplot shows a significant, positive, relationship between percent wear time in VPA and the %CSE_change after high intensity AE. (B) The scatterplot shows a weak, positive relationship between percent wear time in MPA and the %CSE_change after moderate intensity AE, which did not reach significance. (C) The scatterplot shows a weak, positive relationship between percent wear time in LPA and the %CSE_change after low intensity AE, which did not reach significance. The black dotted line indicates the line of best fit; r indicates the Pearson coefficient, p indicates the probability value.

CHAPTER 5: DISCUSSION

This study aimed to determine whether the intensity of the RPA an individual engages in, measured directly by accelerometry, influences the change in CSE that occurs in response to a single session of AE, and whether or not matching the intensity of the AE to that of the RPA influenced this relationship. Participants completed three sessions of AE, on three separate days, adjusted to a low (40% PO_{max}), moderate (60% PO_{max}) and high (80% PO_{max}) intensity. TMS was administered before and after each AE bout at 120% of rMT to assess the change in CSE resulting from the AE. We hypothesized that the greatest increase in CSE would occur when higher percent wear times were accumulated in the same RPA intensity as the AE intensity engaged in, compared to when higher percent wear times were accumulated in an RPA intensity that was not the same as the AE intensity engaged in.

Although the change in CSE after the single high, moderate, and low intensity AE bout was still variable among individuals within the given AE session, certain trends were observed. Overall, the results showed a positive relationship between the $\%CSE_{change}$ after high intensity AE and VPA where CSE was enhanced after high intensity AE. However, no such relationship was observed between $\%CSE_{change}$ after moderate intensity AE and percent wear time in MPA, nor between $\%CSE_{change}$ after low intensity AE and percent wear time in LPA.

Previous studies have shown that an acute bout of AE can induce neuroplastic effects on the brain (El-Sayes, Harasym, Turco, Locke, & Nelson, 2018), with the majority of research involving exercise-induced neuroplasticity in M1. Thus, AE may be an effective adjunct in rehabilitation after a neurological injury is sustained, such as a stroke, as it induces a cascade of neural events which underlie LTP and primes the brain for motor learning and thus functional recovery. Numerous studies have used TMS in an attempt to uncover the mechanisms of this

exercise-induced neuroplasticity, as well as the factors that influence the changes in CSE, to determine the characteristics of AE (and those of the participants engaging in it) that drives this change. Lulic et al. (2017) provided evidence that the level of PA influences this response. Specifically, individuals who self-reported (via the IPAQ) as being highly active showed an increase in CSE after a bout of moderate intensity AE, compared to those who self-reported as being less active. To further characterize participant-level characteristics, MacDonald et. al. (2017) assessed aerobic fitness of their participants (via VO_{2max}) to determine if it influenced the response to AE. Results showed that there was no relationship between VO_{2max} and CSE after a 20-minute bout of moderate intensity AE bout (70% of HR_{max}; McDonald, 2017). In these two previous studies there was a high degree of variability shown with individuals who had high VO_{2max} scores, or individuals self-reported as highly active, having similar CSE responses as their counterparts. Thus, due to VO_{2max} measurement as well as self-reported PA questionnaires being unreflective of one's RPA behaviours, the current study aimed to determine the influence of RPA behaviours on the change in CSE after AE using accelerometry devices for a more object measure of PA.

The differential CSE responses between RPA intensities partially supported our hypothesis, which predicted a greater increase in CSE resulting from the single bout of AE when the intensity of the AE matched the intensity of the particpant's RPA behaviour. Results partially confirmed this hypothesis, as we observed a significant, positive relationship for the $\%CSE_{change}$ after high intensity AE, such that when participants accumulated more percent wear time in VPA, the $\%CSE_{change}$ increased. However, we could not wholly confirm our hypothesis of enhanced CSE when AE and RPA intensities directly matched as the change in CSE after moderate intensity AE was not significantly higher when the participants accumulated more

75

percent wear time in MPA, and the change in CSE after low intensity AE was not significantly

higher when the participants accumulated more percent wear time in LPA.

5.1 Influence of RPA intensity on neuroplasticity.

5.1.1 Implications.

The results indicate that to help create an ideal environment to foster

neuroplasticity (thus priming the brain for motor learning), individuals who accumulated more

time in VPA should engage in high intensity AE for maximal benefit (see Figure 34). These

different CSE responses between RPA intensities may be due to blood lactate concentration

differences as previous research has indicated that blood lactate concentrations after AE can

differ between RPA levels (Moscatelli et al., 2016), influencing CSE. Thus, the results may

reflect differences in the blood lactate threshold among different RPA levels, as individuals with

higher percent wear times in VPA may have a higher lactate threshold compared to individuals

with lower percent wear times in VPA. This higher lactate threshold indicates that the production

of lactate has not exceeded the clearance rate causing lactate to accumulate in the blood, and thus

generates greater increases in CSE. Further, individuals with lower durations in VPA may have

accumulated more blood lactate which can result in music fatigue, diminishing the CSE response

The lower %CSE$_{change}$ after high intensity AE among individuals with lower durations in VPA

may also be due to the novelty and difficulty of the AE task as individuals with lower durations

in VPA have not adapted physiologically to high intensity AE.

5.1.2 Comparing findings to previous research.

Using accelerometer data, our results

partially support Lulic and colleagues (2017) who showed greater enhancements in CSE after

moderate intensity AE (i.e., 50-70% age-predicted HR$_{max}$) among individuals categorized as

'highly' active, compared to individuals classified as 'moderate' or 'less' active who did not

show a change in CSE after moderate intensity AE. The current study shows a trend towards

greater enhancements in CSE among individuals who accumulate more time spent in MPA, however this trend was not significant similar to Lulic and colleagues. Similarly, McDonnell and colleagues (2015) did not show a significant change in CSE among low-moderately active individuals after moderate intensity AE (75% age-predicted HR_{max}). Although both Lulic and colleagues (and McDonnell and colleagues) had individuals engage in moderate intensity AE, it is possible that not all individuals were exercising at a moderate intensity. Both of these studies used the equation: [HRmax = 220-age], which is an inaccurate prediction of HR_{max}, especially for the female participants (Tanaka et al., 2018). Thus, some individuals may have been at a workload harder or lighter than a moderate intensity, depending on abilities (Powers & Howley, 2009), influencing the CSE response obtained. For example, McDonnell and colleagues reported that the actual HR obtained by the individuals was on average 76 +/- 16% during the moderate intensity bout and was reported as 'hard' on the Borg scale. Thus, if an individual in the 'highly' active group was working at a high intensity of AE, the average change in CSE would increase. The results of the current study reinforce this notion that the individual may have been working at a higher AE intensity by showing that individuals accumulating more time spent in VPA had greater enhancements in CSE after high intensity AE, compared to individuals with lower durations in VPA who showed less enhanced CSE. Therefore, the method of calculating the intensity of the AE bout is important in order to reliably conclude the influence RPA levels have on the brain, specifically the motor cortex.

McDonnell and colleagues (2015) also had low-moderately active individuals engage in a bout of low intensity AE (55-65% age-predicted HR_{max}). The actual HR obtained by individuals was on average 58 +/- 5% during the low intensity bout and was reported as 'light' on the Borg scale. Individuals in our study, using a percentage of PO_{max}, reported, on average, the high

intensity AE bout as 'very hard', the moderate intensity AE bout as 'somewhat hard', and the low intensity AE bout as 'very light' on the Borg scale (see Figure 33). Although we observed a positive trend towards enhanced CSE after low intensity AE among individuals who spent more time in LPA, this relationship did not reach significance, similar to McDonnell and colleagues.

Contradictory to Lulic and colleagues (2017), Snow and colleagues (2015) found that a 30- minute bout of moderate intensity AE (60% VO_2peak) had no effect on CSE among healthy individuals who self-reported RPA being moderately or highly active (i.e., >1500 MET mins/week) on the IPAQ. However, the results of the current study support the findings from Snow and colleagues as the 8- minute bout of moderate intensity AE (60% PO_{max}) did not significantly enhance CSE among individuals with more time spent in MPA. The contradictory results between Lulic et al and Snow et al, although both studies used the IPAQ to group individuals as well as moderate intensity AE, reinforces the issues with characterizing RPA levels with a self-reported questionnaire. Thus, when attempting to discern the effect that AE (or more broadly PA) has on the brain, specifically the motor cortex, it is important to use a measure that will accurately measure RPA levels.

5.2   Optimizing interventions for motor rehabilitation.

Improving methods of prescribing AE that will optimize the effectiveness of motor practice is essential for the recovery of sensorimotor function after stroke (Nepveu et al., 2017). This includes the influence of what happens immediately before and after motor practice on the extent to which the individual retains any improvements in motor skill during practice between training sessions, thus determining the speed of the recovery process (Nepveu et al., 2017). Rogers (2018) did not find a significant influence of engaging in HIIT prior to learning a motor skill. Thus, it is unclear whether greater gains can be demonstrated when AE is implemented before or

after a motor task to optimize improvements in learning or retention. Although we did not have participants learn a new motor skill before or after AE, as this would have taken an extensively long time to complete all participants necessary for statistical power, the results of the current study can assist clinicians when implementing AE before or after a motor task to optimize improvements in learning or retention.

Higher levels of PA have been associated with improved health and physical function in those with neurological conditions, such as stroke (El-Tamawy, Abd-Allah, Ahmed, Darwish, & Khalifa, 2014). Clinicians can use accelerometers to gain a patient's PA profile by having them either wear the ActiGraph, or another available device, at home. Measures related to a participants RPA behaviour could indicate that the individual would benefit more from high intensity AE compared to a low, or moderate intensity; thus, facilitating plasticity in the motor system. Multiple electronic devices exist that have an accelerometer within them such as the Fitbit, Garmin, smart watch, as well as smart cell phones via built in Google fit app. Although these devices can inaccurately record activity (e.g., fast walking recorded as biking or jogging), they have been deemed reliable and valid (Diaz et al., 2015), with strong predictive accuracy (Kwapisz, Weiss, & Moore, 2011). These highly consumed products provide an opportunity for clinicians to incorporate them into rehabilitation. Our results can provide further knowledge for what durations are a sufficient dose to facilitate a favourable response in the brain.

AE is prevalent in neurorehabilitation, as it promotes neuroplasticity and improves motor recovery. Among stroke patients, some aspects of cognitive and motor function have been shown to improve after AE. Since AE intensity is suggested to be an important component of improving the influence AE has on neuroplasticity and motor recovery, increasing AE intensities may amplify gains post-stroke (Nepveu et al., 2017). Acute AE can change brain function, improving

cognitive and motor skill acquisition, by enhancing neural activity and heightening attentional systems. This enhanced neural activity increases communication between neurons, allowing for new synapses to be made. However, patients with chronic stroke tend to have a significantly reduced neuroplastic response to acute intense AE such as the HIIT protocol (2-minutes at 25% PO_{max}, followed by 3-minutes at 100% PO_{max}) compared with healthy individuals (Nepveu et al., 2017). Thus, muscle fatigue, or the reduction in muscle performance at a given work rate (Bogdanis, 2012), may play a factor with the reduced neuroplastic response at intense AE bouts. Robust support for changes in muscle metabolism, and thus increased muscle fatigability, among individuals with lower amounts of RPA (i.e., deconditioned; Rimmer, Schiller, & Chen, 2012); compared to increased muscle strength, and thus increased resistance to muscle fatigue, among individuals who chronically exercise (Hurley et al., 2011). Muscle fatigue can influence CSE, explaining the decreases in CSE among individuals high in LPA and MPA after high intensity AE. Further, the decrease in CSE among individuals high in VPA after low intensity AE may have occurred as lower intensities of AE were not sufficient enough to elicit a larger CSE response than before the AE bout, suggesting individuals who regularly engage in VPA have higher thresholds for eliciting CSE due to brain specific adaptations.

The results in the current study showed preferential responses to high intensity AE among individuals who spent more time in VPA, however the %CSE$_{change}$ varied among individuals after each AE intensity (see Appendix 11).

5.3   Limitations and Future Directions

There were several limitations associated with the study that may have impacted the results. Firstly, when performing the TMS assessment, the re-application of the glasses after the AE bout may have slightly altered the co-registration of the TMS system to the participant's

head, resulting in a small change in the location of stimulation from the pre-exercise time point. In addition, the time of day the AE sessions occurred on was not controlled for and changed based on the individual's schedule. Consistency in time of day should be considered in future studies using TMS and AE protocols as cortical inhibition has been shown to decrease as duration awake increases (Lang et al., 2011), and CSE has been shown to increase (Huber et al., 2013), which may influence pre-exercise levels of CSE. Another limitation related to the blood lactate measurements. As indicated previously, the blood lactate values obtained in the study did not appear to be valid as they differed considerably from published norms. Typically, blood lactate levels range between 0.5-1mmol/L (Franklin, 2014), with Ahlgrim and colleagues (2017) finding resting blood lactate levels to be ~1.27 mmol/L +/- .36 mmol/L on average. However, the resting blood lactate levels in the current study was higher than previous studies, ~ 7.21mmol/L on average. Further, at the various time points when blood was collected, three lactate measurements were taken, and each of these measurements tended to be quite different from each other. The fluctuations in blood lactate between measurements may be due to its sensitivity to sweat, or antiseptic residue. Sweat contains lactate, thus if sweat was in the blood sample, it could have resulted in a higher recorded lactate level than the actual amount of lactate in the blood sample (Derbyshire, Barr, Davis, & Higson, 2012). Cleaning the area with an alcohol wipe prior to the finger prick may have diluted the blood sample (EKF Diagnostics, 2019), reducing the concentration of blood lactate, although given the values obtained were considerably higher than published norms, this is not the most likely explanation. Previous research examining the blood lactate threshold found the concentration at one's lactate threshold, on average, to be 2mmol/L (Spurway, 1992). Since our blood lactate levels were much higher than 2mmol/L at baseline, we excluded blood lactate concentrations from the analysis as the validity of this data

was compromised. Future studies may gain more accurate and reliable blood lactate samples using more advanced technology to measure blood lactate levels in the serum and/or plasma.

Another device limitation was associated with the ActiGraph accelerometer. Specifically, this accelerometer was taken off and on throughout the wear time period. Therefore, if an individual took the device off for more than the two- minute spike tolerance, but was still active during the time it was off, the device would have recorded that time period as sedentary rather than active. Also, the calculated average MVPA per day may have been obtained in one or two bouts, thus, a more detailed analysis of the average MVPA per day is needed. Furthermore, the accumulation of lactate may have been faster due to the nature of the AE task, creating the leg muscles to fatigue quickly. This would be experienced among individuals who are not avid cyclers. The sample consisted of two avid cyclists, however most of the individuals did not regularly cycle, making it a novel, and difficult, task for them at higher intensities; shown by individuals higher in LPA decreasing in CSE after high intensity AE. Thus, future research study designs could determine the change in CSE after walking and running on a treadmill. Further, accelerometers have an inherent limitation of tracking PA that does not involve stepping movements, such as cycling, swimming, and kickboxing, as well as upper body limb activities such as yoga, weight lifting/strength training; all of which were activities that most participants reported engaging in during the week the accelerometer was worn (Colley et al., 2012). For the ActivPAL, a cycling bout could be recorded with the 'stepping time' as it would record the leg position changes, however, the ActiGraph on the hip would most likely not record the cycling bout.

The current study was also limited by the size of the sample. Seventeen individuals were shown to be adequate in previous studies to determine statistical significance in the change in

CSE from pre-to- post-exercise (MacDonald, 2017), however a larger sample would have increased the power of the correlation-based analysis (Field, 2013). A greater sample size, and thus increased power, would provide more confidence in the resulting p-value (i.e., whether the influence of RPA intensity on CSE is significant), as having more individuals in the sample would reduce the inter-subject variability present in CSE after AE.

In addition, the diversity in RPA of the sample population was a limitation. The amount of VPA accumulated was quite low (less than 2%). Thus, future studies should aim to recruit a wider range of participants, (perhaps high performance athletes who would accumulate higher durations of VPA), leading to a better indication of the influence of VPA on CSE after AE. Furthermore, it is evident that an individual may have met the recommended guidelines related to PA, but spent the majority of their time sedentary as it is possible to accumulate 150 minutes of MVPA in longer duration, but less frequent, bouts of activity. Since both the ActiGraph and ActivPAL can break the duration of time spent sedentary (which we did not include in the statistical analysis of the present study), future work could consider examining time spent sedentary alongside RPA behaviours to determine its influence on the brain's response to a single session of AE. Since reducing sedentary time can result in health benefits, the duration of a sedentary bout time can possibly have differential effects on CSE, thus future research should investigate the influence sedentary time has on CSE.

Future research can extend this study by investigating whether there are differences in corticocortical connections among individuals with various RPA behaviours (i.e., percent wear time LPA, MPA, and VPA), after low, moderate and high intensity AE using paired-pulse TMS. This type of TMS is used to probe changes in the effectiveness of synaptic connections in the brain, revealing short term plasticity, and AE has been shown to decrease cortical inhibition

(Singh et al., 2014b). For instance, short and long interval cortical inhibition (SICI and LICI respectively), that are indicators of intracortical inhibition, would provide more in-depth knowledge on the GABA receptor activity and neuroplastic changes in M1, and intracortical facilitation (ICF), an indicator of intracortical facilitation, would provide knowledge of NMDA receptor activity. This additional information would provide insight into the short-term changes in CSE and inhibition that occur before the long-term neuroplastic changes underlying motor learning (Nepveu et al., 2017) and whether these changes differ between individuals with different RPA patterns. Furthermore, future studies should determine if RPA behaviours show differential patterns of blood lactate accumulation during a single, continuous, AE bout which gradually increases from a low to high intensity. Examining this relationship would provide insight into how blood lactate concentrations change among individuals of different RPA intensities during AE, and whether these blood lactate levels influence CSE after AE.

In addition, the stationary cycle ergometer may have been a a novel, and aerobically demanding, task for many of the participants, which may have resulted in an underestimation of one's maximal exertion on the GXT (as well as HR_{max}, and VO_{2max} values; Pollock, 2008). For example, the excluded individual for our study stopped the GXT at 100W when her reported perceived exertion was 13 on the Borg scale ('somewhat hard'). This reduces the ability to derive an AE prescription as the measured maximal values, indicating functional capacity, are inaccurate. Thus, treadmills have been used instead to measure one's maximal functional capacity (Pollock, 2008). The CSE responses may be less variable if a treadmill was used for the AE task instead. A more familiar modality may lessen the impact novelty has on enhanced CSE, creating an exaggerated response, and allow for a clearer influence of the different AE intensities

on CSE. Different AE intensities on the treadmill could be derived by increased inclination or increased speed, as a percentage of the individual's maximal capacity.

A common difference between previous studies and our study is the measurement defining the AE intensity. When $\%VO_{2peak}$, or age-predicted HR_{max}, are used to determine the AE intensity it was less likely that all individuals exercising at the target intensity, limiting the accuracy and reliability of the trend in CSE changes after AE. This was confirmed by the range of actual HR_{max} and RPE measures indicating a higher or lower intensity than the goal intensity. By using $\%PO_{max}$ to find the AE intensity, more individuals are likely to exercise at the goal intensity, providing more reliable and accurate trend in CSE changes after AE. It has been stated from studies on healthy individuals that the intensity of AE is crucial for a neuroplastic response to acute exercise to occur (Nepveu et al., 2017). Therefore, PO_{max} should be used to calculate AE intensity in future research, in order to obtain accurate and valid indication of the influence AE has on CSE. Clinicians can also use PO_{max} to determine AE intensity as the GXT is fast and easy to administer.

5.4   Main Conclusions

This study investigated the influence of RPA on CSE after three intensities of AE. The results provide partial support for our hypothesis as participants responded differently between AE intensities depending on their RPA behaviour. Individuals with more time in VPA would benefit from engaging in high intensity AE, whereas individuals with less time in VPA would not benefit from engaging in high intensity AE. However, contrary to our hypotheses, individuals with more time in MPA would not benefit from engaging in moderate intensity AE over those with less time in MPA, and individuals with more time in LPA would not benefit from engaging in low intensity AE over those with less time in LPA. Therefore, individual characteristics can

influence CSE and the intensity of the AE bout is an important consideration when designing an AE program, where the goal is to prime the brain for learning a motor task. Specifically, this research work can assist clinicians by providing insight into optimizing the neurorehabilitation exercise protocol by tailoring the AE intensity to the individuals' RPA characteristics. This research uncovered significant relationships between RPA levels, and CSE, however individuals were still variable in brain responses after AE. Thus, additional research on the influence of other individual characteristics, such as age (>40 years old) and body composition, on CSE is required. Overall, this work generated knowledge related to the effects of AE on brain function and short-term plasticity as well as individual characteristics, such as RPA, that influence this relationship

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Appendix 1: Recruitment Poster

How does Physical Activity affect Brain Functioning?

Volunteers Needed!

We are recruiting for a study using brain stimulation to look at how regular physical activity behavior can influence the brain after aerobic exercise.

You will be asked to wear an accelerometer for 9 days and engage in 3 aerobic exercise (AE) sessions, on separate days.
One of these sessions will determine your maximum heart rate. This will require you to do a maximal exercise test.

The study will also involve transcranial magnetic stimulation (TMS). TMS allows us to look at brain function to measure the properties of the brain, like how easy it is to turn on a particular brain region.

You will be asked to participate in 3 AE sessions, with each session lasting 1.5 hours in total. This study will be performed in the Laboratory for Brain Recovery and Function in the School of Physiotherapy.

You will receive $10 / visit. To be eligible to volunteer, you must be between 18 and 40 years of age and not have any brain, lung or heart conditions. You must also be right-handed and have normal or corrected-to-normal vision.

Who to Contact: Brittany Roberts, Graduate Student
Email: br868524 @dal.ca

Study Title: The relationship between regular physical activity behaviour and brain activity after aerobic exercise.

Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca	Accelerometers & Exercise br868524@dal.ca

Appendix 2: Letter of Information

*Study Title- **The relationship between regular physical activity behaviour and brain activity after aerobic exercise***

Dear participant,

Thank you for your interest in "Examining the Effect of High Intensity Interval Training on Motor Learning"*, a study being conducted by Brittany Roberts, a Masters of Science (Rehabilitation Research) candidate, and Dr. Shaun Boe from School of Physiotherapy at Dalhousie University. We are investigating how regular physical activity behaviors can influence cortical responses after a single bout of aerobic exercise. In order to participate you must:*

- *Be between 18 and 40 years of age*
- *Be right-handed*
- *Have normal or corrected-to-normal vision*
- *Be a non-smoker*
- *Not have an elevated BMI ($\geq 30kg/m^2$) and a large waist circumference (>102 cm for men and >88 for women)*
- *Never have been diagnosed with a cardiovascular, respiratory, or neurological disease*
- *Have never been told that you are not allowed to perform aerobic exercise by your doctor.*
- *Be eligible for non-invasive brain stimulation as per a screening form.*

There are 4 files attached in this email:

- *Two screening forms, called the PAR-Q and the TMS Screening Form. We ask you to* complete these screening forms; if you answer, "yes" to any item on the PAR-Q, or any of the first 9 questions on the TMS screening form, you are ineligible to take part of this study. In this case, email the researcher that you are not eligible (you do not have to tell what is the reason for ineligibility).
- An informed consent form: please read this form as it describes what you will be doing as part of the study, as well as outlines any risks and benefits.
- A questionnaire called the IPAQ that will help us determine your physical activity level (You can have a look at it, but don't worry about filling it out at this time).

If you are eligible to participate in the study, we will ask you wear an accelerometer for 9 days and attend 3 laboratory sessions within a two-week period. The total time commitment, including Day 1, in the laboratory will be ~5.5 hours). Participants will be compensated $10 per visit, whether they complete the session or not. *Participation is voluntary and you are free to withdraw from the study at any time, without consequences. You are not obliged to answer any questions or participate in any activities that you find objectionable or which make you feel uncomfortable. All information we collect is confidential.*

On testing days, we will ask you to please bring clothing you are comfortable in (there will be somewhere private where you may change), to perform cycling exercise.
In preparation for each of the next testing session, we ask that you follow these guidelines:

- Maintain the **similar diet:** eat same amount and same type of food (at the same timing) at least 2 hours before you come to the test.

(e.g. if you're scheduled to start the session at 4 p.m., and you had a light sandwich and a piece of fruit during the time between 2 to 4 p.m., we ask that you have a similar meal and similar portion during the same time, before the next sessions)

- Please refrain from **caffeine, heavy meals, and alcohol** for at least 2 hours before the test as these subtances are known to have effects on the things we will be measuring.

If you are interested in this study or have any questions, please reply to this email and we will arrange a time that is convenient for you. Please feel free to contact br868524@dal.ca *or 1-(519)-280-9593 if you have any questions.*

> *Thank you for your interest,*
> *Brittany Roberts*

Appendix 3: Physical Activity Readiness Questionnaire

2017 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

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

GENERAL HEALTH QUESTIONS

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

✔ **If you answered NO to all of the questions above, you are cleared for physical activity.**
Go to Page 4 to sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

▶ Start becoming much more physically active – start slowly and build up gradually.

▶ Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).

▶ You may take part in a health and fitness appraisal.

▶ If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

▶ If you have any further questions, contact a qualified exercise professional.

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

⚠ **Delay becoming more active if:**

✔ You have a temporary illness such as a cold or fever; it is best to wait until you feel better.

✔ You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.

✔ Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

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01-01-2017

2017 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

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

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

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

2. Do you currently have Cancer of any kind?

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

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

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

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

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

4. Do you have High Blood Pressure?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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☑ **If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:**

▶ It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.

▶ You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.

▶ As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.

▶ If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

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

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

⚠ **Delay becoming more active if:**

✓ You have a temporary illness such as a cold or fever; it is best to wait until you feel better.

✓ You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.

✓ Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

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

PARTICIPANT DECLARATION

● All persons who have completed the PAR-Q+ please read and sign the declaration below.

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

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that the Trustee maintains the privacy of the information and does not misuse or wrongfully disclose such information.

NAME _____

DATE _____

SIGNATURE _____

WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

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

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Appendix 4: TMS screening form

LABORATORY FOR
BRAIN RECOVERY AND FUNCTION
SCHOOL OF PHYSIOTHERAPY
DALHOUSIE UNIVERSITY
Inspiring Minds

TRANSCRANIAL MAGNETIC STIMULATION (TMS) SCREENING FORM

Below is a questionnaire used to determine whether potential participants are suitable for research studies using transcranial magnetic stimulation (TMS). Please complete the questions honestly and to the best of your knowledge. This information, as well as your identity, will be kept completely confidential.

Participants Study ID: _____

Participants Age: _____

PLEASE COMPLETE THE QUESTIONS BELOW   **Yes**   **No**

Do you have epilepsy or have you ever had a convulsion or a seizure?

Have you ever had a head trauma that was diagnosed as a concussion or was associated with a loss of consciousness?

Do you have any hearing problems or ringing in your ears?

Do you have cochlear implants?

Are you pregnant or is there any chance that you might be?

Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?

Do you have a cardiac pacemaker or intracardiac lines?

Do you have a medication infusion device?

Have you ever had a fainting spell or syncope (loss of consciousness)?
If yes, please describe on which occasion:

Are you taking any medications? (please list):

Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, please specify:

Did you ever undergo TMS in the past? If yes, were there any problems:

Did you ever undergo MRI in the past? If yes, were there any problems:

If you answer, "yes" to any of the first 9 ineligible for this study. Please contact the researcher to let them know that you are not eligible; you do not have to tell why you are not eligible. Please bring a list of your medications to the first study visit.

* TMS screening form is from the International Consensus Guidelines:
Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120: 2008-2039.

Appendix 5: Informed Consent

DALHOUSIE UNIVERSITY

LABORATORY FOR BRAIN RECOVERY AND FUNCTION

SCHOOL OF PHYSIOTHERAPY

CONSENT FORM

Project Title: **The relationship between regular physical activity behaviour and brain activity after aerobic exercise**

Dr. S.G. Boe
Associate Professor
School of Physiotherapy
Dalhousie University
(902) 494-6360
s.boe@dal.ca

Brittany Roberts
MSc Candidate
School of Physiotherapy
Dalhousie University
1-(519)-280-9593
br868524@dal.ca

Funding provided by the Natural Sciences and Engineering Research Council (NSERC)

Introduction
You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.
Please read this carefully. Take as much time as you like. Mark anything you don't understand, or want explained better. After you have read it, please ask questions about anything that is not clear.
The researchers will:
Discuss the study with you
Answer your questions
Keep confidential any information which could identify you personally
Be available during the study to deal with problems and answer questions

You are being asked to take part in this study because you replied to our advertisement, you meet the study requirements, and you are free of any brain injury or disease and meet the inclusion criteria for the study.

Purpose and Outline of the Research Study
Exercise has been shown to make strengthening brain connections easier by increasing how excitable the brain is. However, it remains to be determined whether regular physical activity behavior influences brain activity after a given AE intensity. This study will examine how AE can change brain excitability differently based on one's regular

physical activity behavior. The information gathered in this study will tell us a lot about how regular physical activity affects the brain, and how to improve the prescribed dose of aerobic exercise to facilitate learning new skills.

Who Can Participate in the Research Study?

You may participate in this study if you are between 18 and 40 years old, are right-handed, and have no self-reported history of neurological (brain), cardiovascular (heart), or pulmonary (lung) disorders. You must also have normal or corrected-to-normal (that is you wear glasses or contact lenses) vision. Additionally, we will ensure you can undergo all of the study procedures by screening for specific conditions (we describe this below).

You will not be eligible for this study if you:
Are a smoker
Have an elevated body mass index or BMI ($\geq 30kg/m^2$) and a large waist circumference (>102 cm for men and >88 for women)
Have ever been told by your doctor that you are not allowed to perform exercise
Have any conditions precluding participation in non-invasive brain stimulation, as determined by screening

How many people are taking part in the study?

15 individuals will be participating in this study.

What You Will Be Asked to Do?

Screening
You be asked to complete some questionnaires to see if you can take part. This is called screening. It is possible that the screening results will show that you can't be in the study. The research team will discuss these with you.
We will do two screening tests. The first is a questionnaire to determine if you can participate in transcranial magnetic stimulation (TMS; described in the next section). We will be using this technique to assess brain excitability. This set of questions will take about 5 minutes to complete. The answers to the questions will determine whether or not you have any conditions that could possibly cause you harm if you were to have brain stimulation (TMS). The second is a questionnaire to determine if it is safe for you to exercise. This questionnaire, called the PAR-Q, will take about 3 minutes to complete.

Following screening, if you are eligible to participate, you will be asked to attend 3 aerobic exercise sessions (sessions 1-3) over a period of one week for a total time commitment of ~4.5 hours (1.5 hours each session). In these separate aerobic exercise sessions, a single bout of low, moderate, or high aerobic exercise will be performed. Prior to these 3 aerobic exercise sessions you will engage in a graded maximal exertion test on a stationary bike to obtain your maximal power output and heart rate. Afterwards, TMS will be applied to obtain your resting motor threshold. We will then introduce you to two accelerometers that you will wear for 9 days, one taped to your front right thigh with Tegederm and the other around your waist.

After wearing the accelerometers for 9 days, the aerobic sessions 1-3 will occur within a week time period. Sessions 1-3 must be completed within a week, with a day separating each session. All sessions will take place in the Laboratory for Brain Recovery and Function (Dalhousie University).

<u>During the maximal exercise test session (Day 1, 1.5 hours):</u>

You will be asked first to complete the screening forms (PAR-Q and TMS screening form), a Health History Questionnaire and the International Physical Activity Questionnaire (IPAQ) that have been emailed to you and to sign this informed consent form. The Health History Questionnaire will ask questions about your age, sex, height, weight, and the types of exercise you do, if any. The IPAQ will ask you about the time you spent being physically active in the **last 7 days**.

You will then be shown the equipment we will use in the study and you will have a chance to ask any questions. After this, we will direct you to a private change room if you need to change into comfortable clothing for the duration of the test. You will begin the maximal exertion test by sitting on a stationary bike quietly for 5 minutes to measure your resting heart rate. Then, you will start cycling on the stationary bike and your heart rate will be monitored to determine your maximal heart rate for aerobic exercise. The cycling part of this task takes a different amount of time for each person, typically lasting between 15 and 20 minutes. In total, these tasks on Day 1 will last approximately 1.5 hours.

<u>During the brain activity assessment session (session 1-3, 1.5 hours each):</u>
Each of the participants will perform the following testing procedures:
Transcranial Magnetic Stimulation (TMS)
TMS is a machine that uses electricity to create a magnetic field. TMS involves delivering brief magnetic pulses over different locations on your head. Basically, a TMS machine stores electricity and then uses this electricity to make a magnetic field in a small coil that is held over your head. The magnetic field creates a flow of electrical current in your head. We can use TMS to measure the properties of the brain like how easy it is to turn on a particular brain region.

Muscle activity
Activity in your muscles will be measured using electromyography (EMG). EMG involves attaching two electrodes (like stickers) to the skin over the muscles of the forearm. Because of the location of these electrodes, it would be best to wear a short-sleeved shirt for the study

Aerobic exercise (AE) on a stationary bike
AE will be performed on a stationary bicycle and will involve a 5 minute warm-up prior to the aerobic exercise bout followed by a 5-minute cool-down.

Watch to monitor your heart rate ('Mio watch')
The 'Mio watch' is simply a watch that acts as a heart rate monitoring device that allows one to measure one's heart rate in real time or record the heart rate for later analysis.

Blood lactate measurements
To measure blood lactate your finger will be pricked with a small needle and a sample of 2-3 drops of blood will be collected. Band-aids® will be made available as required. Blood samples will be collected before the exercise test (resting value), and at the end of aerobic exercise bout during the post exercise TMS data collection period, for a total of 2 blood lactate measurements each session. Three finger pricks will be applied for each measurement, with 18 finger pricks in total over the three sessions.

Overview of sessions 1-3
As you arrive, you will be asked to sit in a reclined position on a chair and the TMS coil will be positioned on or near your head. You will be asked to keep your head as still as possible. This procedure is not painful. You will hear a clicking noise as the current flows through the coil. When determining the position of the TMS coil, the pulses may cause your finger to move. You may also feel some tingling sensations on the head where the TMS coil is located. During this part of the study, we will record muscle activity from your hand as we have described above. Following this, you will experience magnetic pulses for approximately 5 minutes. We will ask you to wear disposable earplugs (which we will provide) while you receive the magnetic stimulation to protect your hearing from the clicking noises.

After you finish the TMS session, you will complete low, moderate, or high intensity AE (plus 5 min warming-up and 5 min cooling-down). Throughout we will monitor your heart rate using the Mio watch (outlined above). As you finish cycling, you are going to transfer back to the TMS chair to let us take the brain measurements again. This time we will take brain measurements immediately after you finish the aerobic exercise bout. After this is done, the testing is completed. In total, each AE session will last approximately 1.5 hours.

Possible Benefits, Risks, and Discomforts
BENEFITS:
Regular exercise has a number of general health benefits including improvement in cardiovascular and respiratory function, reduction in cardiovascular disease risk factors, and overall decreased morbidity and mortality. Exercise can benefit the brain as well; aerobic exercise benefits memory and cognition, can decrease anxiety and depression, and reduces risk for Alzheimer's disease and dementia. Although these benefits result from regular exercise, a single session of activity can have benefits as well; a single session of exercise can improve your insulin sensitivity, lower your blood triglyceride levels, as well as lower your blood pressure.
This study has the potential to benefit society through the generation of knowledge regarding the effect of aerobic fitness and exercise on the brain, as well as the effect of exercise on learning a new skill.

RISKS:
Presented here are the potential risks and discomforts that may arise throughout the duration of the study:

Potential risks during Maximal Exercise Testing:
Nearing the end of the exercise test, you will experience shortness of breath, muscular fatigue, and an increased heart rate, while dizziness, nausea, muscular pain and profuse sweating may occur. These symptoms should subside as soon as the test is over, or shortly thereafter. If these symptoms persist or worsen, investigators qualified in first aid response will monitor the

participants' condition and call for medical assistance if required. Some solutions to help reduce symptoms include slowly walking around, small sips of water or lying down with the legs elevated above the heart. An active cool down period is prescribed to alleviate any symptoms arising from the maximal exercise. The cool down period will be considered complete when the heart rate of the participant falls below 50% of their age-predicted maximum heart rate. Studies have shown that only an average of 2.4 in 10000 participants will experience any adverse outcomes from this protocol that will require immediate medical treatment and this represented a population of variable health.

Potential risks of using TMS:
TMS has been approved in Canada for both therapeutic and research use, and has been used in various studies worldwide since 1985. TMS has been shown to be extremely safe as long as proper safety precautions are taken. In general, the TMS procedure produces no pain and causes no known short-term or long-term damage of any kind. We will contact you if any new risks are discovered during the time of this study. Please contact us if you experience any effects that you feel may be a result of your participation in the study.
TMS is painless, although some forms of TMS can cause tingling or twitching of muscles in the face, which may lead to soreness. This is not likely to occur in this study, as we are not using that form of TMS.

Common risks: 1-10% people have experienced headaches, which are caused by muscle tension. In the case of a headache, you will be advised to take whatever pain medication you usually take for mild headaches, which in most cases promptly resolves the discomfort.

Rare risks: .01-.1% people have experienced the following:
In rare cases, seizures have been known to occur after TMS. However, the risk of seizure is *very low* except in people with epilepsy or people taking certain medications. You will be asked to complete a TMS screening form, and precautions will be taken to ensure your safety. Despite these precautions, TMS can induce a convulsion even in people who do not have brain lesions, epilepsy or other risk factors for seizures. However, only 16 cases of convulsions induced by TMS in participants without risk factors for epilepsy have been reported despite the fact that many thousands of subjects have been studied world-wide. The overall risk for seizures during TMS is thought to be less than 1 in 1,000 patients. As with seizures in general, the seizures induced by TMS are usually brief and without serious physical consequences. In total, only 2 instances of seizure have been reported in participants undergoing the forms of magnetic stimulation that will be used during this study. In both of these cases, the participants were diagnosed with a neurological disorder and each were taking medications that alter brain excitability.

As indicated above, TMS produces a loud clicking noise when the current passes through the coil. This loud click can result in tinnitus and transient decreased hearing if no ear protection is used. To prevent this adverse effect both the TMS operator and participants wear earplugs during the application of TMS. Studies have shown that earplugs can effectively prevent the risk of hearing disturbances.

TMS is generally safe unless you have metal or magnetized objects in your body. Examples of these metal objects are cardiac pacemakers, surgical clips (e.g., aneurysm clips in your head),

artificial heart valves, cochlear implants, metal fragments in your eyes, electronic stimulators, and implanted pumps. If you have any of these, you will not be able to participate in this study.

<u>Potential risks of recording muscle activity (EMG)</u>
There is minimal risk related to the use of this technique. The electrodes lie on top of the skin (like a sticker on your skin) and a conductive gel provides the contact between the skin and the electrodes. In uncommon instances (.01- .1%) it is possible that your skin may be sensitive to the conductive gel, alcohol or adhesive used in the application of the electrodes. In such cases a rash or reddening of the skin is possible. This usually goes away in less than 24 hours.

If for any reason we find information that may show a possible health risk, we will explain the issue to you and strongly recommend that you visit your family doctor. You will no longer be eligible to participate in the study.

What you will receive for taking part:

There is $10 per session given to participants taking part in this research study. This money is meant to cover the cost related to travel to the lab sessions and will be provided regardless of whether you complete the session or not. Juice and snacks will be provided after you complete the session.

How your information will be protected:
Privacy: Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. No identifying information (such as your name) will be sent outside of Dalhousie University. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.
If you decide to participate in this study, the research team will look at your personal information and collect only the information they need for this study, such as your;
Name
Age
Biological sex
Information from the study questionnaires

Confidentiality: In order to protect your privacy and keep your participation in the study confidential, you will be de-identified using a study code. For the purpose of data analyses, all participants will only be identified by their study code (e.g. s001). All hard copy data associated with the study (including this consent form) will be stored in a locked cabinet in a secured laboratory that is accessible only to lab personnel via personalized pin codes and who are trained in confidentiality. All data collected will be stored on a secure, password-protected server in the Laboratory for Brain Recovery and Function. No documentation will exist (hard copy or electronic) that links your name with your study code.

Data retention: Information that you provide to us will be kept private. Only the research team at Dalhousie University will have access to this information. We will describe and share our findings in theses, presentations, public media, journal articles, etc. We will be very careful to only talk about group results so that no one will be identified. This means that **you will not be identified in any way in our reports**. The people who work with us have an obligation to keep all

research information private. Also, we will use a participant number (not your name) in our written and computer records so that the information we have about you contains no names. All your identifying information will be securely stored. All electronic records will be kept secure, password protected server in the Laboratory for Brain Recovery and Function.

If You Decide to Stop Participating
You may choose not to continue your participation in the study at any time. If you decide not to take part in the study or if you leave any session early, your data will be automatically withdrawn from the study. If you complete your session, your data may be withdrawn up until the point of data analysis.

How to Obtain Results
If you would like a description of the results at the end of the study, you can obtain a short description of these results by visiting boelab.com in approximately 12 months. You may request data related to your maximal exercise testing from the investigator. Otherwise no individual results will be provided.

Questions
We are happy to talk with you about any questions or concerns you may have about your participation in this research study. Please contact Brittany Roberts at Br868524@dal.ca or 1-(519)-280-9593 or Dr. Shaun Boe at s.boe@dal.ca or (902) 494-6360 at any time with questions, comments, or concerns about the research study. We will also tell you if any new information comes up that could affect your decision to participate.

If you have any ethical concerns about your participation in this research, you may also contact Catherine Connors, Director, Research Ethics, Dalhousie University at (902) 494-1462, or email: ethics@dal.ca
Signature Page

Project Title: *The relationship between regular physical activity behaviour and brain activity after aerobic exercise*

Lead Researcher:
Shaun Boe, MPT, PhD

Signature Page

I have read the explanation about this study. I have been given the opportunity to discuss it and my questions have been answered to my satisfaction. I agree to take part in this study. However I realize that my participation is voluntary and that I am free to withdraw from the study at any time.

_____   _____
Participant's Signature   DATE

_____   _____
Print Name of Participant   DATE

_____
_____
Signature of Witness   DATE

Appendix 6: Health History Questionnaire

1. Age: _____

2. Sex
   a. Male
   b. Female

3. What is your approximate weight (kilograms)? _____
   To convert from pounds to kilograms, multiply by 0.454

4. What is your approximate height (meters)? _____
   To convert from inches to meters, multiply by 0.0254

5. Please calculate your approximate BMI (*you will be provided with a calculator*):
   BMI = height/ weight^2 = meters/ (kg*kg) = _____

6. At any point in the last 6 months were you a regular smoker?
   a. Yes
   b. No

7. If you do any exercise, what types of exercise do you do? Please be specific
   (i.e.running, swimming, soccer, basketball, etc.)

   _____

   _____

   _____

Appendix 7: Borg Rating of Perceived Exertion (RPE) Scale

Rating	Perceived Exertion
6	No exertion
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Appendix 8: Physical Activity and Sedentary Behaviour Questionnaire

CSEP-PATH: PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR QUESTIONNAIRE (PASB-Q)
ADULT (18 AND OVER)

Please answer the following questions based on what you do in a typical week. To increase accuracy, you may wish to log your physical activity and sedentary behavior for one week prior to answering the questions.

Aerobic Physical Activity

1. Frequency: In a typical week, how many days do you do moderate-intensity (like brisk walking) to vigorous-intensity (like running) aerobic physical activity ?

____ days/week

2. Time or Duration: On average for days that you do at least moderate-intensity aerobic physical activity (as specified above), how many minutes do you do?

____ minutes/day

Total: Multiply your average number of days per week by the average number of minutes per day.

____ minutes/week

Muscle Strengthening Physical Activity

3. In a typical week, how many times do you do muscle strengthening activities (such as resistance training or very heavy gardening)?

____ times/week

Perceived Aerobic Fitness

4. In general, would you say that your aerobic fitness (ability to walk/run distances) is:

____ Excellent   ____ Very Good   ____ Good   ____ Fair   ____ Poor

---

Sedentary Behaviour

5. On a typical day, how many hours do you spend in continuous sitting: at work, in meetings, volunteer commitments and commuting (i.e., by motorized transport)?

☐ None ☐ < 1 hour ☐ 1 to < 2 ☐ 2 to < 3

☐ 3 to < 4 ☐ 4 to < 5 ☐ 5 to < 6 ☐ > 6

6. On a typical day, how many hours do you watch television, use a computer, read, and spend sitting quietly during your leisure time?

☐ None ☐ < 1 hour ☐ 1 to < 2 ☐ 2 to < 3

☐ 3 to < 4 ☐ 4 to < 5 ☐ 5 to < 6 ☐ > 6

Total Sedentary Behaviour (add responses to questions 5 and 6)_____ hours/day

7. When sitting for prolonged periods (one hour or more), at what interval would you typically take a break to stand and move around for two minutes?

☐ < 10 minutes

☐ 10 to < 20 minutes

☐ 20 to < 30 minutes

☐ 30 to < 45 minutes

☐ 45 to < 1 hour

☐ 1 to < 1.5 hours

☐ 1.5 to < 2 hours

☐ > 2 hours

# Appendix 9: Daily Activity and Wear Log (modified from O'Brien & John, 2017).

ActiGraph Daily Log Sheet

Day (M/D/Y)	Time woke up	Went to Bed	Was the device removed during wear time (circle one)	If Yes, during what time?	Did you remove the device a second time? If so, what time?	Total Wear Time	Activity	Duration	Intensity
Example: Day 1: September 30th, 2018	*8:45am*	*11:30pm*	*No* / *Yes*	*2:00pm to 3:00pm*	*No*	*14.5 hours*	*Walking*	*30 minutes*	*Moderate*
Day 1:			No / Yes						
Day 2:			No / Yes						
Day 3:			No / Yes						
Day 4:			No / Yes						
Day 5:			No / Yes						
Day 6:			No / Yes						
Day 7:			No / Yes						
Day 8:			No / Yes						
Day 9:			No / Yes						

Appendix 10: Assigning random numbers with RAND() in Excel and ordering sessions

Participant	Low Intensity	Moderate Intensity	High Intensity	Session 1	Session 2	Session 3
1	0.18045526	0.95250033	0.51860359	LI	HI	MI
2	0.98890525	0.85757019	0.48915774	HI	MI	LI
3	0.91709576	0.4836179	0.80354128	MI	HI	LI
4	0.3093545	0.88116764	0.79712529	LI	HI	MI
5	0.83212254	0.10088881	0.86720103	MI	LI	HI
6	0.57633558	0.77540256	0.77358903	LI	HI	MI
7	0.01942232	0.4620817	0.04435453	LI	HI	MI
8	0.32909692	0.44874396	0.48243406	LI	MI	HI
9	0.86410349	0.32394813	0.00259514	HI	MI	LI
10	0.8203933	0.73319843	0.78183899	MI	HI	LI
11	0.54998631	0.50080567	0.19393429	HI	MI	LI
12	0.98794155	0.97906084	0.93106527	HI	MI	LI
13	0.15752573	0.88223121	0.36537233	LI	HI	MI
14	0.0530308	0.4746971	0.56987449	LI	MI	HI
15	0.2121093	0.91861503	0.43223773	LI	HI	MI

Appendix 11: Individual variability in CSE after AE

A

B

C
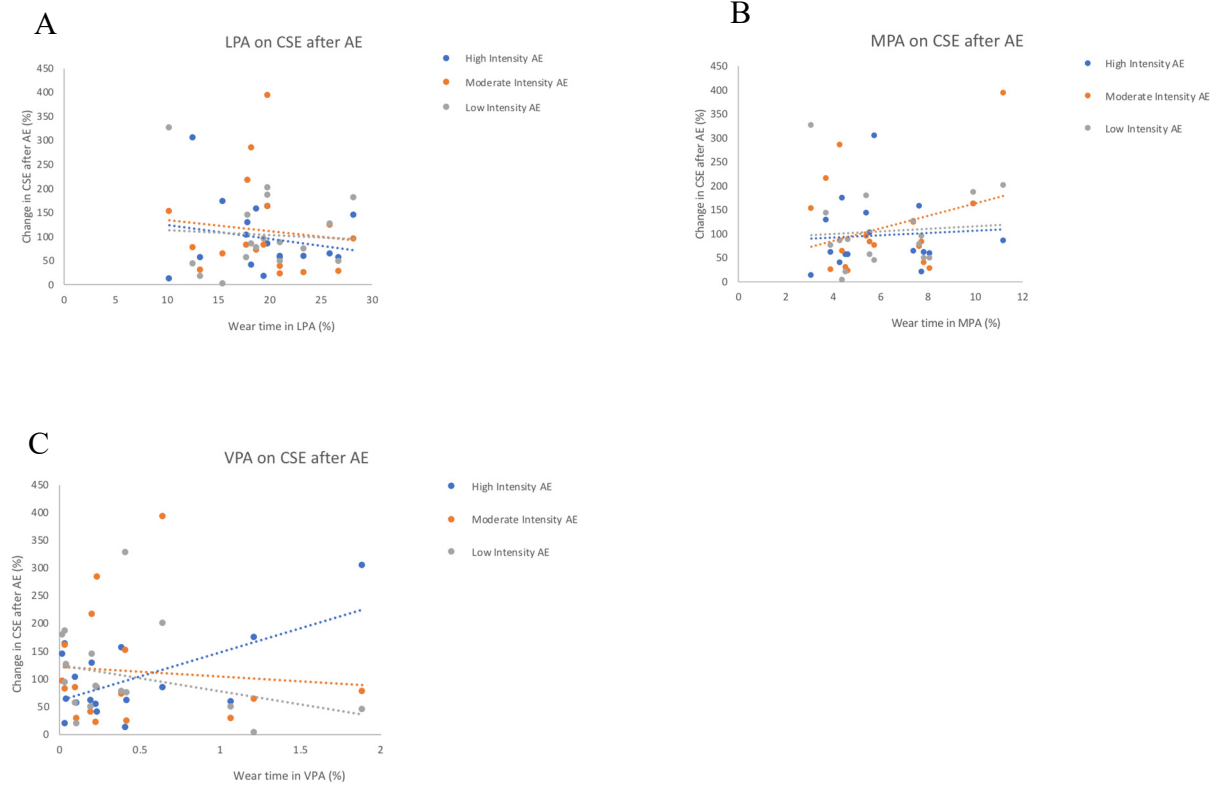
Note. Blue dots indicate $\%CSE_{change}$ after high AE, orange dots indicate $\%CSE_{change}$ after moderate AE, and grey dots indicate $\%CSE_{change}$ after low AE, with the corresponding dotted lines representing the trend line of best fit. (A) shows the relationship between increasing percent wear time in LPA and enhances in CSE after low and moderate AE. (B) shows the relationship between increasing percent wear time in MPA and enhances in CSE after high AE. (C) shows the relationship between increasing percent wear time in MVPA and enhances in CSE after low, moderate, and high AE.