INVESTIGATING THE EFFECT OF AEROBIC EXERCISE ON CORTICOSPINAL EXCITABILITY: A SCOPING REVIEW

By

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ABSTRACT

Background/Aim: Emerging evidence suggests aerobic exercise (AE) enhances corticospinal excitability (CSE). The aim of this scoping review was to characterize evidence on whether acute AE increases CSE in healthy and post-stroke individuals. A sub-objective was to investigate AE characteristics that affect CSE. **Methods:** After searching four databases, studies examining the effect of a single bout of AE on CSE were identified and screened, and data extracted, tabulated, and characterized. **Results:** Seventeen studies matched the inclusion criteria. Overall, moderate intensity AE led to an increase in CSE among healthy individuals. In participants post-stroke, this effect was only observed following high intensity AE. **Conclusion:** In healthy individuals, moderate intensity AE induced CSE; however, neither low nor high intensity did. While the intensity was the most important factor, duration, modality, and participant characteristics also influenced the findings. Comparative studies are needed to further characterize the optimal AE conditions to enhance CSE.

LIST OF ABBREVIATIONS USED

ACSM – American College of Sports Medicine

AE - Aerobic Exercise

BDNF - Brain-Derived Neurotrophic Factor

CASP - Critical Appraisal Skills Programme

CBF- Cerebral Blood Flow

CSE - Corticospinal Excitability

EMG- Electromyography

fMRI- Functional Magnetic Resonance Imaging

GABA- Gamma-aminobutyric Acid

GXT - Graded Maximal Exercise Test

H-Reflex – Hoffman Reflex

HR_{max} - Maximum Heart Rate

HRR- Heart Rate Reserve

I/O- Input output curve

ICF - Intracortical Facilitation

IGF-I - Insulin-like Growth Factor

IPAQ - International Physical Activity Questionnaire

LICI - Long-Interval Intracortical Inhibition

LTD - Long-Term Depression

LTP - Long-Term Potentiation

M1 - Primary Motor Cortex

MEP - Motor Evoked Potential

MET - Metabolic Equivalent

MVC- Maximum Voluntary Contraction

NMDA - N- methyl – D- aspartate

NZ-PAQ - New Zealand Physical Activity Questionnaire

PA - Physical Activity

PAR-Q - Physical Activity Readiness Questionnaire

PRISMA- Preferred Reporting Items for Systematic Reviews and Metanalyses guidelines for scoping reviews

RHR- Resting Heart Rate

RMT - Resting Motor Threshold

RPE- Rate of Perceived Exertion

rTMS - Repetitive Transcranial Magnetic Stimulation

SE- Spinal Excitability

SICI - Short-Interval Intracortical Inhibition

SMA-Q - Sports Medicine Australia Questionnaire

S-R - Stimulus-Response

TMS - Transcranial magnetic stimulation

VEGF - Vascular Endothelial Growth Factor

VO_2 peak - Peak Oxygen Uptake

VO_{2max} - Maximal Oxygen Consumption

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CHAPTER 1: INTRODUCTION

1.1 Skilled Movement and Motor Learning

The ability to perform skilled movement is a fundamental aspect of human life. Skilled movements form the basis of many activities ranging from activities of daily living through to recreational activities and occupational performance. Skilled movements are acquired or improved through the process of motor learning. Motor learning is the process of acquiring new skills, or optimizing series of actions for achieving specific tasks (Monfils, Plautz, & Kleim, 2005). Motor skill learning can be divided into several stages which include acquisition, retention, and consolidation. Each stage requires changes in the structure and function of the brain (Dayan & Cohen, 2011). These alterations in the brain can include changes to neurons, synapses, and neural networks across or within specific brain areas. In fact, the brain remodels its neural circuitry continuously to enable behavioral change and encode new experiences (Black, Jones, Nelson, & Greenough, 1997; Grossman,Churchill, Bates, Kleim, & Greenough, 2002).

The ability of the brain to change its structure throughout our lifetime is the basis of learning and adaptation (Ramirez & Arbuckle, 2016). Experiences influence the brain by adjusting the organization and the activity of a particular neural circuity. Synaptic plasticity is the activity- (or experience-) dependent alteration of neuronal activity, namely the modification of the efficacy or strength of synaptic transmission (Citri & Malenka, 2008). With each instance of learning something new or trying to acquire a new skill, the brain is physically changing as it stores this new information and a memory is generated (Ramirez & Arbuckle, 2017; Criti & Malenka, 2008). Ultimately, repetition of the skill to be learned

modifies the synaptic strength through activity-dependent processes, resulting in long-lasting changes.

Specifically, the brain has billions of neurons which are interconnected with each other by synapses to compose the neural circuits. The synapse is the site of communication between two neurons, and the location where plasticity can occur. As indicated by the psychologist Donald Hebb, neurons that "fire together, wire together," meaning that if activation of a presynaptic neuron results in activation of the postsynaptic neuron, the strength of the connection between these neurons will be increased over time. This model is often referred to as Hebbian learning (Attneave, B., & Hebb, 1950). In contrast, if activation of the presynaptic neuron does not result in activation of the postsynaptic neuron, the strength of the connection between these two neurons will decrease. These processes are referred to as long-term potentiation (LTP) and long-term depression (LTD) respectively (Lüscher & Malenka, 2012).

Depolarization of the presynaptic neuron results in the release of an excitatory neurotransmitter known as glutamate, which in turn acts on two receptors on the postsynaptic neuron: N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazo-lepropionic acid (AMPA) (Lüscher & Malenka, 2012). As indicated, both receptors are activated by glutamate; however, the NMDA receptor has a unique characteristic that when the cell is at resting potential, the channel is blocked by a magnesium ion. (Ramirez & Arbuckle, 2016). The magnesium ion is displaced when the cell is slightly depolarized – via preceding activation of the AMPA receptor –, which allows the channel of the NMDA receptor to open. The activation of the NMDA receptor triggers a complex signaling cascade that forms the basis of LTP, which begins with the

influx of calcium, that leads to, among other things, the insertion of additional AMPA receptors on the postsynaptic membrane (Ramirez & Arbuckle, 2016). Increasing the number of AMPA receptors on the postsynaptic membrane can amplify the impact of the excitatory current, resulting in the postsynaptic neuron being more likely to activate. The activation of AMPA and NMDA receptors in this manner provides a demonstration of the mechanism by which Hebbian learning can occur, providing evidence that the firing of neurons can lead to increase the strength of the synapse (Ramirez & Arbuckle, 2016).

As indicated above, the process of learning requires the connection between neurons to become stronger. The long-lasting changes described above that are produced by neuronal activity, and which enhance synaptic strength, are known as the basis for skill learning. Much evidence supports this process in driving motor skill learning; for instance, Sanes and Donoghue (2000) found that LTP in the primary motor cortex (M1) underlies motor learning in animal studies. This phenomenon highlights the important molecular and cellular mechanisms associated with motor skill learning and memory formation (Purves et al., 2004, p.583; Martin et al, 2000; Pastalkova et al, 2006; Whitlock et al,2006). In the 1970s, Bliss and colleagues revealed that activation of the excitatory synapses repetitively in the hippocampus resulted in a modification in synaptic strength that lasted for hours or days (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). As mentioned above, the opposing phenomenon of LTP is LTD, where the synaptic strength becomes depressed (Purves et al., 2004, p.583). LTD can be elicited through a prolonged, repetitive low frequency stimulation (Lüscher & Malenka, 2012), while LTP can be achieved by repetitive high frequency stimulation (Purves et al., 2004, p.585).

It has been found that enhancing brain excitability helps plasticity to occur. That in turn drives motor learning which improves motor performance. A study conducted by Perez and colleagues (2004) evaluated the effect of motor skill training on cortical excitability of the leg representation in M1 using transcranial magnetic stimulation (TMS). Twenty-five healthy individuals participated in a visuo-motor training task which consisted of 32 min of voluntary motor skill training, non-skill, and passive skill training sessions. Participants were asked to voluntary perform ankle dorsiflexion and plantarflexion movements to follow six randomized figures that were presented to them on a computer screen. In the non-skill training session, participants were asked to complete continuous voluntary dorsiflexion and plantarflexion movements. However, for the passive training, the movements were performed by the researchers manually. Subjects were instructed to perform the movements eight times for 4 min with rest blocks of 2 min intermixed. The results of the study showed a significant improvement in motor performance with decreased error following the 32 min of motor skill training, but no improvement was observed following the non-skill or passive skill training sessions (Figure 1). The researchers also reported an increase in cortical excitability as evidence by an increase in the amplitude of the motor evoked potential (MEPs) obtained via TMS following the motor skill training session; consistent with the performance change, no increase in excitability was observed for the other two training session types (Figure 2).

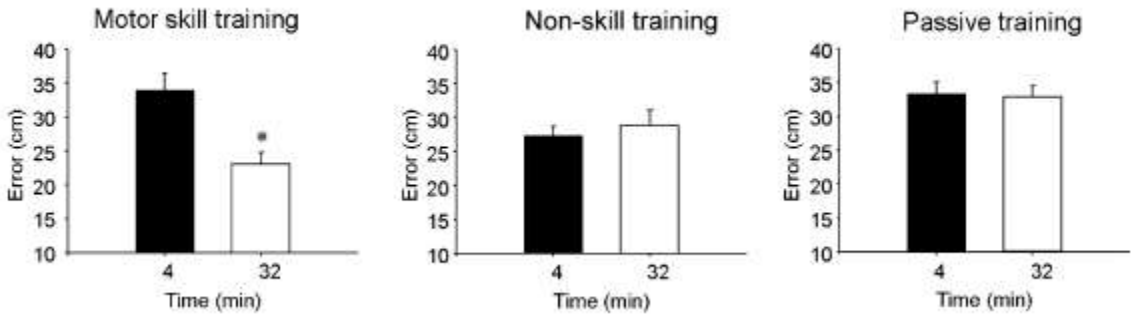

Figure 1. Change in motor performance prior to and immediately after training (from Perez et al., 2004). An improvement in motor performance was observed after motor skill learning evidenced by decreased error in comparison to the non-skill and passive training sessions. Bars represent standard error (*$p<0.05$)

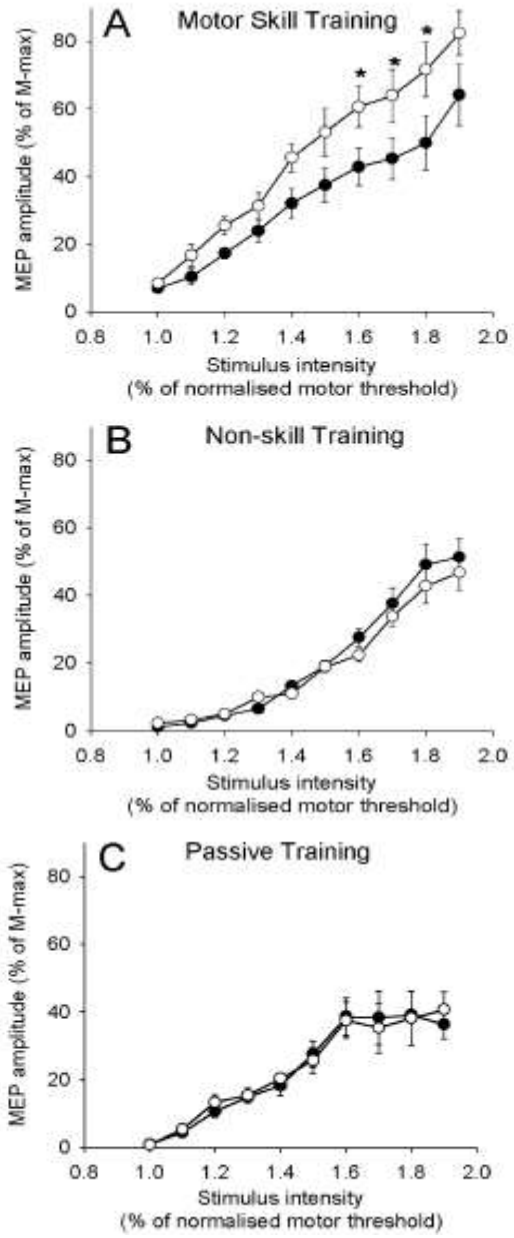

Figure 2. The effect of training session (motor, A; non-skill, B; and passive, C) on leg cortical plasticity. MEPs were obtained from the tibialis anterior muscle prior to (closed circles) and post (open circles) 32 min training sessions. Bars represent standard error (*$p<0.05$).

1.2 Neuroplasticity and Rehabilitation

Rehabilitation has a critical role in re-establishing function lost to injury, and re-learning skills. Indeed, rehabilitation has proven to be an effective method for reducing impairment and improving function (Hatem et al., 2016). As indicated by Kleim and Jones (2008) the ability of the brain to reorganize and change post-injury (i.e., neuroplasticity) is a critical component in the rehabilitation process after neurological injury.

As indicated above, the mechanism underlying the acquisition of new skills or re-acquisition of skills lost to injury is based on the concept of plasticity: "neurons that fire together, wire together". The primary approach used in neurorehabilitation, task-oriented (or task-specific) training, utilizes repetitive task practice of the skill to be learned to drive brain plasticity, resulting in improved function (Arya, Pandian, Verma, & Garg, 2011; French et al., 2007 ; Hubbard, Parsons, Neilson, & Carey, 2009). A study conducted by Hubbard et al. (2015) examined the effect of various intensities of task-specific training on upper limb recovery and brain activity. Twenty-three participants who experienced a first ever ischemic stroke which resulted in motor impairment of the upper limb were randomly assigned into a standard care group, or intensive, task-specific training. The standard care consisted of an average of 31.5 min of physiotherapy and occupational therapy within a mean of 11.5 days, where the intensive training group conducted an additional 30 hours of UL task-specific training within the first month post-stroke which consisted of 2 hours per day, 5 days a week for three weeks. Measurements were taken before the intervention, one-week post-stroke, one-month post intervention, and then again after three months. The measurements of interest that related directly to upper limb functional recovery included the upper limb component of the motor assessment scale (UL-MAS). Findings revealed

that all participants showed a significant increase in motor function of the upper limb over the three months post-stroke; however, participants who were in the intensive training group showed more consistent recovery of the upper limb that was associated with the consistent activation of motor regions in the brain (i.e., supplementary motor area and cerebellum) as measured by functional magnetic resonance imaging (fMRI).

As has been shown above, it is clear that motor skill learning results from repetitive practice that drives changes in the brain (neuroplasticity) from both a structural and functional perspective. Further, the changes in the brain that result from this repetitive task practice form the basis for the techniques used in neurorehabilitation to promote functional recovery. Owing to the importance of motor skill learning in both non-disabled populations and following neurological injury, finding ways to optimize plasticity, and in turn the learning process, could have important implications in many fields. Knowing that neuronal activation is a necessary pre-requisite for synaptic plasticity, altering the excitability of neurons may represent a means of optimizing plasticity. Indeed, the state of a neuron, or its excitability, impacts on the probability of an action potential being generated and the neuron discharging. Neuronal excitability can be altered between resting, hyperpolarized or depolarized states (Steriade, Nuñez, & Amzica, 1993; Cossart, Aronov, & Yuste, 2003), with the position along this continuum determined by the sum of excitatory or inhibitory inputs (Robinson, 1992). More specifically, the state is determined by the interaction of neurotransmitters and cellular receptors that ultimately impact on neuronal excitability (excited or inhibited), that is achieved by controlling the flow of ions through ions channels directly (Badawy, Loetscher, Macdonell, & Brodtmann, 2012). Neurotransmitters influencing excitability include glutamate and GABA (gamma-aminobutyric acid), which

provide excitatory and inhibitory influences respectively, as well as a host of other neuromodulatory agents (e.g., brain-derived neurotrophic factor; discussed below). In-line with the notion that neuronal excitability is a necessary pre-requisite for plasticity, it has been shown that more excitable neurons need to be stimulated less than depressed neurons to induce an action potential and ultimately the desired behavioral response (e.g., muscle activity) (Rossini & Rossi, 2007 ; Badawy, Loetscher, Macdonell, & Brodtmann, 2012) .

In line with the above, the way of changing the excitability of a given neuron or grouping of neurons is by altering the neuron's environment. For instance, excitation can be achieved by increasing the magnitude of excitatory inputs and/or removing or decreasing the magnitude of inhibitory influences. The idea of altering the excitability of the brain to produce an environment that is conducive to plasticity is not new; indeed, various techniques have been used to achieve this. Among the numerous means by which excitability can be altered include caffeine (Specterman et al.,2005), drugs, neuromodulatory techniques, and various forms of exercise, including aerobic exercise. Broadly, the notion of altering the excitability of the brain to create an environment that is conducive to plasticity occurring has been referred to as 'priming' the brain.

1.2.1 Factors that Facilitate Cortical Excitability

Phillis , Edstrom, Kostopoulos, & Kirkpatrick (1979) indicate that caffeine is a methylxanthine that is an antagonist to the depressant effect of adenosine, and thus leads to automatically increase in the excitability of cortical neurons. Supporting this notion, Peris & Dunwiddie (1985) indicated that caffeine interacts with neurotransmitters in the brain. Acute caffeine intake induces the transmission of glutamate at the level of the pre- and post-synaptic neuron (Vyleta & Smith, 2008). In the context of movement and M1, an

increase in glutamate release and use at the level of the pre- and post-synaptic neuron leads to an increase in the input to the pyramidal neurons that give rise to the corticospinal tract and ultimately result in enhancement of corticospinal excitability, as assessed via TMS (discussed in detail below). Other approaches to altering excitability in the brain include drugs such as dextro-amphetamine, a CNS stimulant, which can be used alongside neurorehabilitation to facilitate functional recovery after neurological injury (Feeney, Gonzalez, & Law, 1982). Ziemann, Tam, Bütefisch, & Cohen (2002) found that amphetamine enhances neural excitability but decreases long lasting stimulation-induced plasticity in M1. Another strategy to induce changes in cortical excitability is through neuromodulatory techniques (Schabrun & Chipchase, 2012). These techniques can include, but are not limited to, repetitive TMS (rTMS) and transcranial direct current stimulation (tDCS). Both techniques alter excitability via a common mechanism, which is to introduce electrical current into the target tissue, resulting in the resting membrane potential of the neuron to move towards either hyper- or de-polarization depending on the paradigm employed. For instance, TMS delivered at frequencies between 5-20 Hz (Fitzgerald et al., 2006) result in excitation of the target tissue (increases in cortical excitability) (Fitzgerald et al., 2006). Both techniques are painless and considered to be non-invasive (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

While the different approaches covered above have been shown to be effective in altering excitability, each has limitations and drawbacks that include unwanted side effects (e.g., amphetamine, caffeine) and lack of widespread availability or low feasibility of use in clinical settings (e.g., TMS). Interestingly, the responsiveness of the human central nervous system, in this case “excitability”, can change greatly with exercise. Aerobic

exercise (AE) has been shown to benefit not only general fitness and the cardiorespiratory system, but also to have extensive benefits on the brain. Studies have shown that physical exercise is a significant part of life that improves brain function and physical health throughout the lifespan (Hillman, Erickson, & Kramer, 2008). As stated , over the long term, within the individual's brain, AE can contribute to enhanced neural survival and density among those who are physically active (Cirillo, Lavender, Ridding, & Semmler, 2009). Conversely, a lack of engaging in exercise and movement can have an adverse effect on individual's health which results in a decrease in brain function and performance (Hillman et al., 2008).

1.3 Assessing Changes in Neuronal Excitability: TMS

Understanding the level of excitability in the brain, and how it changes in response to different interventions, can inform on the ideal means to increase excitability and, in turn, improve motor skill learning. Assessment of changes in neural activity can be achieved through various neuroimaging techniques; however, the most common means to assess cortical excitability is TMS. As indicated above, TMS is a non-invasive brain stimulation technique which provides an investigation of the cerebral cortex functional state (Ferreri et al., 2011). A TMS system comprises capacitors that store the electrical charge (Valero-Cabré, Amengual, Stengel, Pascual-Leone, & Coubard, 2017a), and a stimulation coil that contains copper wire through which an electrical current passes, producing a magnetic field and ultimately a secondary electrical current that can be delivered into the brain (Valero-Cabré, Amengual, Stengel, Pascual-Leone, & Coubard, 2017b), The basic principle of TMS is the induction of the electromagnetic field in the brain's electrical field (Griskova, Höppner, Ruksenas, & Dapsys, 2006) (Figure 3). TMS

relies on Faraday's Law, which is the passed current in the first coil produces a magnetic field in the other coil, adjacent to it (Golaszewski & Nardone, 2018). In TMS, the first coil is the copper wire, and the second coil is the brain tissue (Golaszewski & Nardone, 2018).

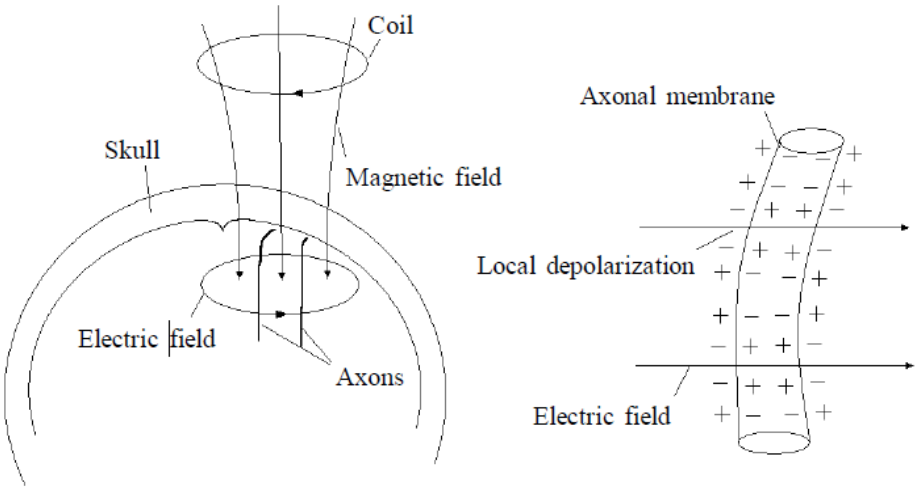

Figure 3. Basic principle of TMS. The flow of ions brought about by the electric field induced in the brain alters the electric charge stored on both sides of cell membranes, depolarizing or hyperpolarizing neurons (Rossi et al., 2009); Retrieved from Griškova (2006).

The current passed through the copper wire in the TMS coil generates a magnetic field that if rapidly changing enough, induces an electrical field sufficient to stimulate neurons, or, depending on the stimulation paradigm, it can change the resting membrane potential of the neurons within the area of stimulation. (Barker,1991; Jalinous, 1991). In its most basic application, the stimulating coil is applied on the scalp overlying a motor representation in M1, and a current is passed through the coil. The current passing through the coil generates a magnetic field "perpendicular to the coil" (Zaghi, Heine, & Fregni, 2009) which passes through the skull inducing a secondary electrical current in the neurons

that are under the coil (Figure 4), resulting in the depolarization of the neurons and action potential generation (Griskova et al., 2006; Ebmeier & Lappin, 2001; Pascual-leone & States, 2014) (Figure 5).

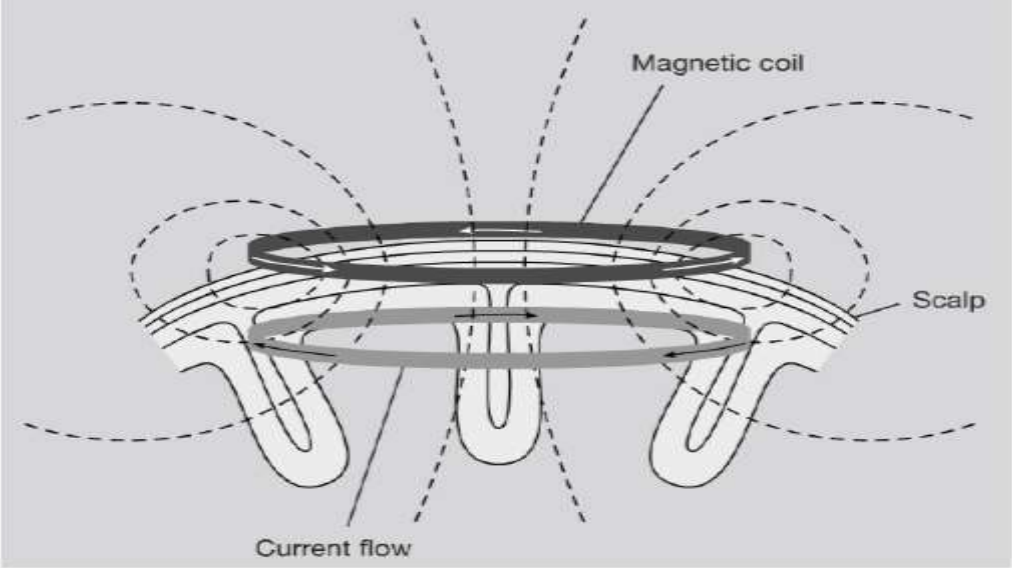

Figure 4. Explanation of electrical current flow in TMS (retrieved from Hallett, 2000). The black solid circle indicates the magnetic field induced by passing the current through TMS coil (perpendicular to the coil), where the grey circle indicates the current induced into the brain. The intermittent lines show the electrical field induced (perpendicular to the magnetic field).

The generation of the action potential from TMS results in a muscle twitch (when the stimulation intensity is above motor threshold) which can be captured and measured by electromyography (EMG). The muscle response to stimulation captured via EMG, called a motor evoked potential (MEP), occurs in the muscle corresponding to the targeted representation in M1 contralateral to the side of stimulation (Figure 5) (Hallett, 2007). The presence of an MEP, as well as its amplitude or area measurement, reflect the integrity of the corticospinal tract (Kobayashi& Pascual-Leone, 2003), and provide an indirect measure

of the excitability of the corticospinal tract (Ferreri et al., 2011). The amplitude and latency of the resulting MEPs are determined by the combination of inhibitory and excitatory inputs at multiple levels along the corticospinal tract (Ferreri et al., 2003; Rossini and Rossi, 2007).

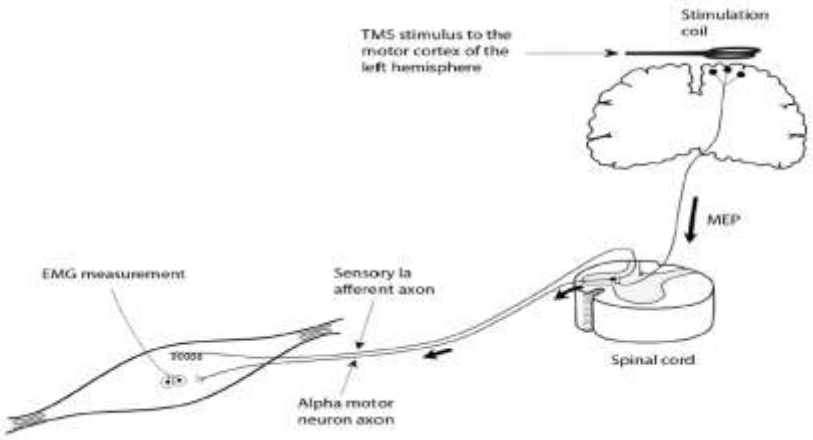

Figure 5. Depiction of the pathway and method for assessment of corticospinal excitability using TMS. When a stimulus is introduced to the motor cortex (via TMS), a muscle response can be produced. Measurement of this muscle response can be achieved using electromyography (EMG). The response to stimulation obtained using EMG is termed a motor evoked potential (MEP), the amplitude of which provides an indication of corticospinal excitability. Retrieved from Alm, 2017.

While there are various forms of TMS, including single-pulse, paired-pulse and rTMS, each achieves a different goal: rTMS is used to alter the excitation of cortical networks (Klomjai et al., 2015), paired-pulse TMS is used to assess the state of intra (or inter) cortical inhibitory and facilitatory networks, whereas single-pulse TMS reflects the excitability of the corticospinal pathway (Singh & Staines, 2015). Thus, the form that will be examined in the present work is single-pulse TMS. As indicated above, the delivery of single stimuli (i.e., a single-pulse) can be used to assess corticospinal excitability, or

changes in corticospinal excitability resulting from various interventions, including AE (McDonnell et al., 2013) , as it causes the neurons in M1 to discharge (depolarize) an action potential. Single-pulse TMS can be applied at a fixed intensity (expressed as a percentage of stimulator output of resting motor threshold, described below), or at varying intensities to generate a stimulus response (SR) curve.

Estimation of corticospinal excitability changes can be detected by various TMS measures including a change in MEP amplitude (as indicated above), stimulus-response (S-R) curve, or at a fixed intensity of resting motor threshold (RMT). The stimulus-response curve is also known as the input-output curve or the recruitment curve (Abbruzzese & Trompetto, 2002). The S-R curve plots the growth of the MEP size (Abbruzzese & Trompetto, 2002), or the muscle response (i.e. twitch) that is evoked by the stimulation at different intensities applied to the same site on the scalp (Unit & Square, 1997). Van der Kamp et al. (1996) and Ikoma et al. (1996) previously reported use of the slope of the curve as an indication of the cortical excitability. Moreover, this curve has a sigmoidal shape, and it represented by various features such as the threshold, steepness, and the plateau level (Abbruzzese & Trompetto, 2002). However, application of single-pulse TMS at fixed intensity relative to the RMT (120% RMT) is often used to measure corticospinal excitability and changes in response to interventions (Fujiyama et al., 2012; Meesen et al., 2011; Vaalto et al., 2011).The fixed intensity of 120% RMT, situated in the middle of the curve, was found to be sensitive to detect the changes happening in the corticospinal excitability pathway (Cuypers, Thijs, & Meesen, 2014).

1.4 Modifying Neuronal Excitability Using AE

Aerobic exercise is the planned repetition of designed physical activity at appropriate intensity to maintain or improve physical fitness (Mackay-Lyons et al., 2012). Physical activity is the body movements that are produced by the exercised skeletal muscles with the release of energy (Caspersen et al., 2018). Aerobic exercise is a form of physical activity of low to high intensity that depends primarily on the aerobic energy-generating process (Plowman & Smith, 2014). Interestingly, the priming of the brain and driving neuroplasticity can be influenced by AE (Ploughman, 2009), as it has been shown to induce neuroplasticity in the brain, and as such may be an important component in the rehabilitative approach for individuals who have experienced a neurological disorder (El-Sayes, Harasym, Turco, Locke, & Nelson, 2019)

Aerobic exercise can promote M1 neuroplasticity (i.e., induced neuroplasticity in the motor cortex) (Cirillo et al., 2009), yet, the mechanism by which AE induces neuroplasticity is not well understood (El-Sayes et al., 2019). Evidence to date shows that AE acts widely within the brain, beyond the regions of the brain that comprise the representation of the muscles/joints engaged in the exercise. Research to date indicates that AE also triggers cellular and molecular processes which support neuronal plasticity (Knaepen, Goekint, Heyman, & Meeusen, 2010). Aerobic exercise promotes changes at different levels of organization, including molecular, cellular, structural, and functional. These changes manifest as a change in behavior (El-Sayes et al., 2019). At the molecular level, AE increases neurotrophins including insulin-like growth factor (IGF-I), brain-derived neurotrophic factor (BDNF) (Schinder & Poo, 2000), and vascular endothelial growth factor (VEGF) (El-Sayes, Harasym, Turco, Locke, & Nelson, 2019). One must

understand the effects of these neurotrophins on the neurons to understand how AE influences neuroplasticity. As mentioned previously, neuronal activity is modifiable, and synaptic transmission efficacy is flexible (Schinder & Poo, 2000). These neurotrophins are a family of proteins that are identified as the mediators for neural differentiation and survival throughout the development of the brain (Ploughman, 2009). Recently, neutrophins have been shown to preserve the viability of neurons over the course of adulthood, protecting the neurons and restoring them in response to ageing and injury (Ploughman, 2009). Moreover, neurotrophins act as modulators of activity-dependent synaptic plasticity (Schinder & Poo, 2000). Neeper et al. (1995) explained that regular AE can increase levels of BDNF, which is a key agent that mediates plasticity in the brain, particularly in the hippocampus, a region in the brain that plays a key role in memory formation among others (Gottschalk et al., n.d.) In support of this claim, the mechanistic effect of AE on the brain was examined in previous systematic reviews, with findings showing that moderate intensity exercise (10 m/min, 5–7 days per week for about 30 min) applied after stroke (24 to 48 hours) in an animal model increases neurotrophin concentration, stimulates synaptogenesis and dendritic branching, as well as protects the perilesional tissue against damage from oxidation and inflammation (Austin, Ploughman, Glynn, & Corbett, 2014; Ploughman, Austin, Glynn, & Corbett, 2015).

Changes at the cellular level within the brain such as neurogenesis, synaptogenesis, and angiogenesis result from an increase in neurotrophin concentration resulting from AE. Neurogenesis is defined as the generation of new neurons in the vertebrate brain over the life span (Colucci-D'Amato & di Porzio, 2008). Van Praag and his colleagues, 1990 emphasized that neurogenesis in the hippocampus is improved by physical activity in

animal models. Lista and Sorrentino (2010) defined synaptogenesis as the creation of synapses between neurons, showing that as a result of chronic exercise, synaptogenesis tends to be improved. Cotman, Berchtold, & Christie (2007) and Sutoo, & Akiyama (2003) showed that BDNF plays a role in neurogenesis and regulation of synaptic growth (Acheson and others, 1995; Binder and Scharfman, 2004) via weakening of the neurotransmission of GABA (Binder and Scharfman, 2004; Kowianski and others, 2017) and improving the neurotransmission of glutamate (Binder and Scharfman, 2004). Finally, angiogenesis reflects the formation of new blood vessels, which like neurogenesis and synaptogenesis, is enhanced by chronic exercise (Lista and Sorrentino, 2010). The mechanism underlying angiogenesis is the up-regulation of VEGF resulting from exercise, as VEGF plays a critical role in the growth of the cerebral vasculature. As well, the up-regulation of IGF-I resulting from exercise has a significant effect on angiogenesis (Cotman, Berchtold, & Christie,2007; Sutoo, & Akiyama, 2003).

The molecular and cellular changes induced by AE that are detailed above are fundamental to the changes observed in brain structure arising from AE. In addition to these changes, a review done by El-Sayes, Harasym, Turco, Locke, & Nelson (2019) indicated that it has also been shown that exercise is correlated with an increase in gray matter volume in the hippocampus, and that engagement in chronic exercise increases white matter volume in the occipital, parietal, and frontal lobes. As indicated previously, exercise leads to changes in brain structure and function, both of which are evidence of plasticity that results from exercise. Functional changes in the brain are characterized by alterations in receptor and neural activity. Examining these changes either in the context of a task or in the resting state can be assessed using TMS. There is further evidence that AE

enhances communication between regions of the brain, suggesting that it enhances the development of synapses between neurons, strengthening the neural networks in the brain. In support of this, resting-state fMRI has revealed that acute AE enhances communications among brain areas. A study by Rajab and colleagues (2014) evaluated resting-state functional connectivity pre- and post- a session of moderate intensity cycling exercise (70% of age-predicted maximum heart rate; HR_{max}) for 20 min using fMRI. They found that functional connectivity increased following AE, particularly between the regions associated with tactile processing and motor function. Also, it has been shown that the activity in thalamic-caudate areas increased post-exercise, as these areas are implicated in motor learning and reward.

1.4.1 Exercise facilitates behavioral change

Aerobic exercise has been shown to facilitate changes in behavior, and specifically in the area of motor performance and cognition. For instance, Snow and colleagues (2016) showed that AE facilitated the acquisition of a motor skill. Sixteen healthy adults performed a continuous tracking (CT) task for 5 min as a baseline; then, participants were randomly assigned into two experimental conditions two weeks apart: one session of moderate intensity cycling (60% peak O_2 uptake) for 30 min, or they were asked to rest (seated position) for the same amount of time. Following the intervention, participants immediately performed the CT task using their non-dominant hand. The task was then repeated after 24 hours to assess skill retention. The experiment showed that the exercise group had better performance following training on the first day of the experiment; however, this difference was not maintained at the retention session (24 hours later). The researchers concluded that a single session of moderate intensity AE was able to change

skill performance compared to a period of rest. As detailed above, it is proposed that AE facilitates improved motor performance and cognition owing to its ability to create an environment in the brain that favors neural plasticity (Ploughman, 2008), including the up-regulation of neurotrophins and blood supply to the brain. A study conducted by Singh, Neva, and Staines, (2016) assessed whether AE and a bimanual visuomotor training task would induce motor excitability similar to a motor learning task using single-pulse TMS. Twenty-five individuals participated in this study. Participants were divided into two groups: training and exercise. The exercise group performed two experimental conditions: exercise (EX), and exercise followed by a training task (EXTR). Briefly, the motor (training) task required wrist flexion/extension to move two handles attached to a potentiometer that controlled the position of a cursor on the monitor; the left-hand handle allowed the participant to move the cursor in the horizontal direction, while the right-hand handle allowed the participant to move it in the vertical direction. The task started when a flashing box appeared on one of three randomly chosen locations on the monitor, then the cursor was visible 2 sec later. At that point, the participant moved the cursor by performing a simultaneous wrist extension movement using both handles to move the cursor to the target location. The participants were encouraged to move the cursor to reach the target as accurately and ~~as~~ quickly as possible. Feedback with a response time would appear once the target was reached. The training session consisted of 160 self-paced trials. TMS was then applied and the amplitude of the resulting MEPs obtained pre- and post-20 min of moderate intensity cycling exercise (65–70% of age-predicted HR_{max}). The same measurements were recorded for the visual-motor training task (i.e., pre and immediately post the training session). The authors found that performing AE accompanied by training

induced enhancement of the brain region underlying task performance (i.e., the areas in the 'central zone', the region responsible for the movement, had increased cortical excitability) compared to training alone (Figure 6). Hence, adding AE to the motor training task can promote cortical changes and create an area which is responsive to the experience-dependent plasticity.

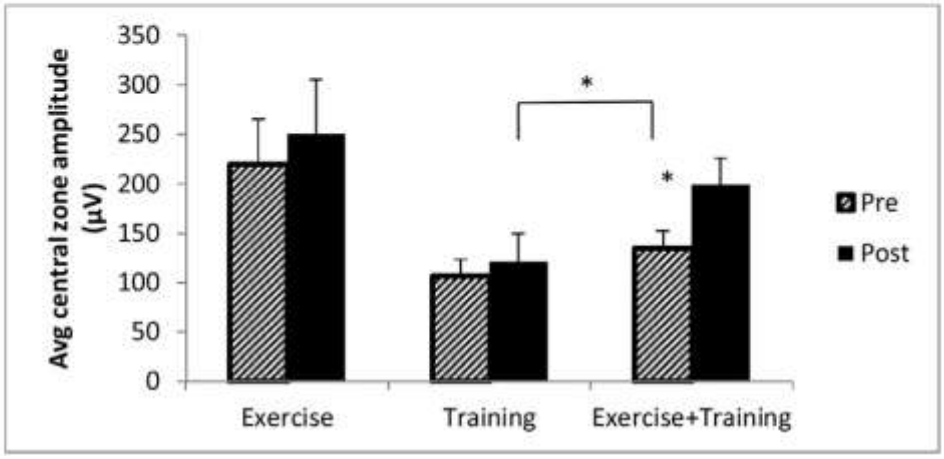

Figure 6. Change in cortical excitability prior to and immediately after training and exercise in the extensor carpi radials (ECR) muscle representation (from Singh, Neva, and Staines, 2016). There was an increase in cortical excitability after exercise + training in comparison to training alone. Bars represent standard error (*$p<0.05$).

1.4.2 Aerobic exercise and excitability

As proposed above, AE can influence the responsiveness of the central nervous system, including alterations in excitability at both cortical and spinal levels (McNeil, Butler, Taylor, & Gandevia, 2013). Singh et al. (2014) examined whether a moderate intensity cycling exercise session influenced excitability changes in a non-exercised upper muscle using TMS (single and paired pulse). Twelve healthy individuals with moderate activity levels participated in the study. In the exercise session, the participants performed

20 min of exercise on a stationary bike at 65-70% of their age-predicted HR_{max}. TMS measurements were taken at baseline, immediately post- exercise (post 1) and then again 30 min post-exercise (post 2). The experimenters used 10 single pulses to generate the stimulus response curves at 100%, 110%, 120%, 130%, and 140% of RMT. Three paired-pulse techniques were performed to determine the effect of AE on short intercortical inhibition (SICI) which is mediated by GABAa receptors, long intercortical inhibition (LICI), and intercortical facilitation (ICF) which is mediated by the ionotropic glutamate NMDA receptors. In summary, the authors observed that there was a significant inhibition of SICI at 30 min post-exercise and increase in ICF. However, the S-R curve showed that corticospinal excitability was not modified as a result of the AE, as there was not a significant change in MEP amplitude at any intensity of stimulation. The authors concluded that the effect of the cycling exercise (using lower limb muscles) was not limited to the exercised muscles. Despite the fact that there was no direct change in the excitability of the non-exercised muscles, modulating the balance of the excitatory and inhibitory inputs of the pyramidal cells (SICI and ICF) was observed. These conclusions indicate that AE may have significant impact on plasticity and, in turn, have clinical utility with regard to neurorehabilitation.

Following up on the work of Singh and colleagues, Lulic et al. (2017) examined the effect of 20 min of cycling at a moderate intensity (60% of the age-predicted HR_{max}) on corticospinal excitability where the participants were divided into two groups based on their physical activity level (high or low). In this study, the authors found that there was a significant increase in excitability in the 'High' physical activity group compared to the 'Low' physical activity group post the session of moderate intensity cycling exercise. The

results suggest that AE has significant effects on M1 which can increase the potential for neural plasticity to occur. The researchers emphasize that AE has the ability to enhance corticospinal excitability following a single session of exercise, and they argue that one session of moderate intensity cycling exercise can contribute to drive the excitability changes in M1. In previous work from our laboratory (MacDonald et al., 2019) the effect of varying intensities of AE on corticospinal excitability was examined, including: low (30% of heart rate reserve, HRR, which approximates to 57% HR_{max}), and moderate (40% and 50% HRR, which approximates to 64% and 70% HR_{max}, respectively). It was examined whether the low intensity AE would induce any enhancement or changes within M1 using single-pulse TMS. TMS measurements were recorded pre-and post-exercise. Participants completed 20 min of cycling exercise at the different intensity levels on separate days. The results indicate that there was a significant change in corticospinal excitability post-exercise at the moderate intensity levels, but not following the lower intensity exercise (30% HHR; Figure 7).

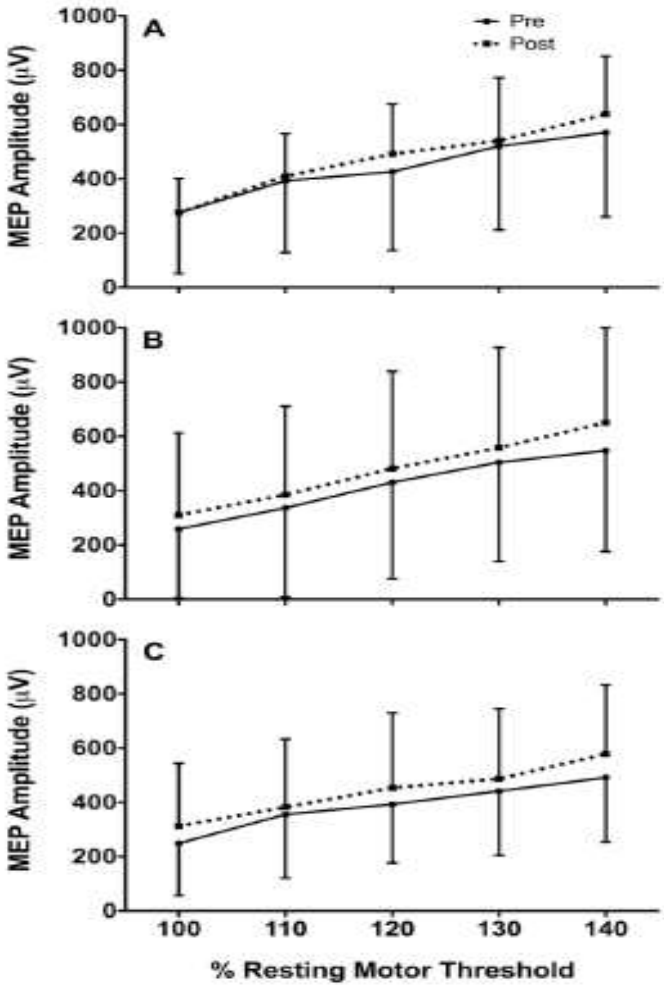

Figure 7. Stimulus response (S-R) curve showing changes in corticospinal excitability prior to and immediately after AE at 30% (A), 40% (B), and 50% of HRR (C); from MacDonald et al., 2019). An increase in corticospinal excitability was observed after 40% and 50% HRR, but not after AE at 30% HRR. Bars represent standard deviation.

In contrast, Mooney and colleagues (2016) conducted a study to examine the response of a single session of moderate intensity AE on changes in corticospinal excitability. The participants cycled at (60% of peak oxygen uptake, VO_2 peak) for 30 min, with changes in corticospinal excitability assessed using single-pulse TMS. Results showed that there were no significant changes in corticospinal excitability after the session of cycling exercise compared to the pre-exercise measurements. Another study conducted by Smith and others (2014) evaluated whether a single session of low to moderate, or

moderate to high intensity, AE increases corticospinal excitability. Participants cycled at a low to moderate intensity (40% of predicted HRR) or at a moderate to high intensity (80% of predicted HRR) for two blocks of 15 min. Changes in corticospinal excitability (using S-R curves) were tested using single-pulse TMS. Findings indicated that there were no changes in corticospinal excitability following a bout of cycling exercise either at low to moderate, or moderate to high intensity. Similar findings were shown with participants who have experienced stroke. Murdoch, Buckley, and McDonnell (2016) examined the effect of a single session of cycling exercise on corticospinal excitability. Twelve chronic stroke survivors (at least 6 months post-stroke) participated in the study. Measurements of corticospinal excitability were evaluated using single-pulse TMS, with baseline measures taken before the exercise and then again immediately post and at 10-, 20-, and 30-min post-exercise at 120% of RMT. Participants cycled at low intensity (at a cadence of 50 RPM) for 30 min. Their findings showed that there was no significant effect of low-moderate intensity AE on corticospinal excitability (Figure 8).

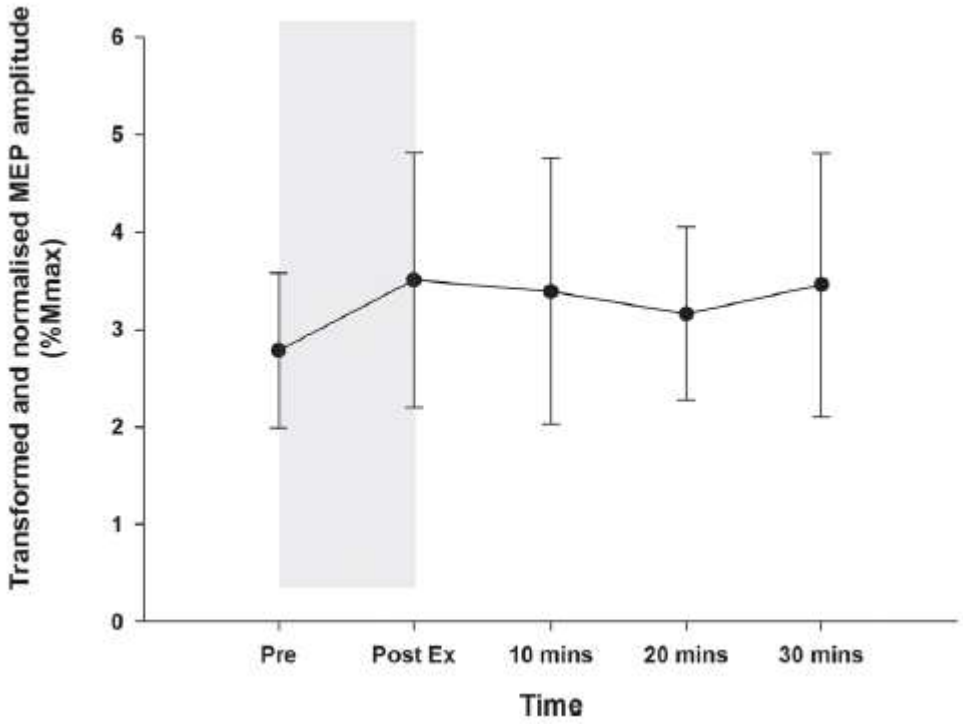

Figure 8. Changes in cortical excitability (MEP amplitude) prior to and after exercise (from Murdoch et al., 2019). There were no changes in cortical excitability observed post-exercise at any time point (immediately-post, 10 min, 20 min, or 30 min-post exercise) at low intensity compared to baseline. Bars represent standard deviation.

As detailed in the literature review above, it has been found that AE has significant effects on the brain. However, some studies showed there was a change in the excitability post a single session of AE, while some do not show any significant changes. Indeed, there is variability in the brain's response to AE with different exercise protocols across the studies. Thus, this is an emerging area of research, and reviewing the literature to determine the trend in the effect of AE on excitability is needed. Given this, the present scoping review aims to explore the effect of AE on corticospinal excitability within healthy individuals and individuals who have experienced stroke; as well as to identify key factors

or characteristics of AE parameters that impact on corticospinal excitability (i.e., increasing the corticospinal excitability).

A scoping review is a type of research synthesis that aims to map the literature and available evidence on a certain research area or relevant topic (Daudt, van Mossel & Scott, 2013; Arksey & O'Malley, 2005). There are various purposes and indications for scoping review, for instance to examine emerging evidence that is unclear (Armstrong, Hall, Doyle, & Waters, 2011), or to provide an opportunity to identify key factors related to a field, and to address knowledge gaps in the research (Munn et al., 2018).

As indicated above, changes in excitability can happen along the corticospinal tract, evidenced by work from McNeil, Butler, Taylor, & Gandevia (2013) who state that AE can influence the responsiveness of the central nervous system, including alterations in excitability at both cortical and spinal levels. As such, should an adequate number of research studies that assess both cortical and spinal level excitability be retrieved following the database search, a secondary objective of the review would be address is whether the change in excitability observed post-AE occurs in the brain or the spinal cord, or at both sites.

1.5 Cortical versus Spinal Level Excitability

As detailed above, TMS can be used to assess excitability of the corticospinal tract, with some research showing that an acute bout of AE increases excitability. When considered in the context of using AE to 'prime the brain', the majority of the literature discusses the effect of AE at the cortical level (i.e., changes in the brain proper), yet the majority of the literature assesses corticospinal tract excitability, which includes two sites where excitability can be modulated: at the cortical level and the spinal level. Like

pyramidal neurons in M1, alpha motor neurons in the spinal cord are subject to excitatory and inhibitory inputs (i.e., glutamatergic and GABAergic inputs among other neurotransmitters), and thus changes in excitability which manifest at the level of the muscle (assessed via the MEP) are not distinguishable between the cortical and spinal level using TMS alone. Given this, assessing spinal level excitability in addition to excitability of the entire corticospinal tract can help to identify at which level AE induced changes in excitability are occurring. This point is far from trivial given the purported role of AE in creating an environment in the brain that facilitates plasticity and motor skill learning.

Spinal-level excitability can be determined via measurement of the Hoffman reflex (H-reflex). The H-reflex reflects the estimation of the spinal alpha motoneuron excitability (Zehr,2002); The H-reflex is widely used as a clinical tool and in motor control research, as it can be elicited over many muscles whose nerve supply can be accessed for percutaneous electrical stimulation (Misiaszek, 2003). Additionally, the H-reflex is commonly used in exercise studies to investigate modulation of spinal-level excitability (Grosprêtre & Martin, 2011).

Similar to the H-reflex is the stretch (tendon-tap) reflex; both are considered monosynaptic and have the same arc path (Misiaszek, 2003 ; Palmieri, Ingersoll, & Hoffman, 2004). The difference between these two reflexes is that the stretch reflex can be induced following a muscle stretch whereas an electrical stimulation is applied to evoke the H-reflex. From a mechanism perspective, the H-reflex is obtained after applying a sufficient electrical stimulation to a peripheral mixed nerve (Schieppati,1987) (i.e., sensory and motor nerve) that generates an action potential that travels along two directions: orthodromically, or toward the muscle; and antidromically, or toward the spinal cord,

which produces an early muscle response (termed the M-wave) and a late response (H-reflex) obtained via EMG.

Spinal-level excitability is influenced by different factors, including exercise. A study conducted by Neva and colleagues (2017) assessed the effect of cycling exercise on corticospinal excitability and spinal-level excitability of a non-exercised upper limb muscle (abductor pollicis brevis; APB). Ten participants engaged in 20 min of moderate-intensity stationary cycling (65-70% of age-predicted HR_{max}). Corticospinal excitability (MEPs) and spinal-level excitability (H-reflex and V-wave) measurements were recorded before and immediately after exercise. Briefly, in contrast to the H-reflex, the V-wave is produced at supramaximal stimulation intensity of a mixed nerve (McNeil, Butler, Taylor, & Gandevia, 2013), and is recorded during a voluntary contraction (Upton et al., 1971). In this particular study, Neva et al. (2017) showed that the V-wave reflects the response obtained from the electrical stimulation over the median nerve when the participant was performing a maximal hand grip contraction (100% maximum voluntary contraction; MVC). In measuring corticospinal excitability, 10 stimuli were given at each stimulus intensity ranging from 100 to 140% of RMT, then an MEP recruitment curve s was obtained. Spinal-level excitability was obtained from the APB muscle by giving 7 to 10 stimuli until the M-wave reached its maximum (Mmax). Then, participants were asked to make a light contraction (10% of MVC) at which 20 trials were performed during which the H-reflex response was obtained before and after exercise. The findings revealed that there was no significant difference in MEPs post- compared to pre-exercise. Additionally, the H and V-waves did not change post-exercise. Similar finding were observed in (Yamazaki et al., 2019) studies, that spinal excitability did not change following a single session of low

intensity AE. The authors examined whether an acute pedaling exercise at a low intensity (30% of VO_2 peak) modulates changes in spinal excitability within exercised and non-exercised limbs as assessed using the F-wave. Briefly, the F-wave is a late response that develops at a supramaximal electrical stimulation (Brown et al., 2002); the F-wave differs from the H-reflex as it is a direct reflection of the alpha motorneuron in that it does not traverse sensory (i.e., afferent) fibers, as its volley results from the antidromic impulses that travel along the motor fibers (McNeil, Butler, Taylor, & Gandevia, 2013). Fourteen participants pedaled for 30 min, with F-wave and M-max amplitude measurements taken pre and 5-, 20-, 40- and 60-min post exercise from the first dorsal interosseous muscle (upper limb non-exercised muscle), and the tibialis anterior (lower limb exercised muscle) using electrical stimulation. Results showed that there were no significant changes in spinal excitability over time post-exercise within either the exercised limb or non-exercised limb.

Overall, there is still limited evidence and there is no extensive work that demonstrate whether the effect of moderate intensity AE mediates a change at the cortical or spinal level, or if changes occur at both. Thus, in addition to the primary objective of exploring the effect of AE on corticospinal excitability, a secondary objective for this work is to investigate the site of these changes.

CHAPTER 2: STUDY OBJECTIVE AND RESEARCH QUESTION

The objective of this scoping review is to investigate the available evidence on corticospinal excitability changes resulting from AE among healthy individuals as well as individuals who have experienced a stroke. Given that recovery following brain injury depends on plasticity, and that plasticity is facilitated when the brain is in the excitable state, we opted to also examine the effect of AE on corticospinal excitability within the stroke population. Overall, the review aims to:

- Explore whether an acute bout of AE drives an increase in corticospinal excitability, and if so, what factors influence this.
- Explore whether increases in corticospinal excitability in response to an acute bout of AE occur at the cortical or spinal level, or both.

Research Question

Our primary question is:

In healthy adults, does engaging in an acute bout of AE drive an increase in corticospinal excitability?

Secondary Questions:

1- In individuals who have experienced stroke, does engaging in an acute bout of AE drive an increase in corticospinal excitability?

2- Does engaging in an acute bout of AE drive an increase in cortical or spinal level excitability, or both?

Sub-Question:

What are the characteristics of AE that result in an increase in corticospinal excitability?

CHAPTER 3: METHODS

3.1 Search Strategy and Data Sources

To access and retrieve the available evidence related to the effect of an acute bout of AE on corticospinal excitability, a comprehensive search of pertinent databases was performed. No limit was placed on the years, in that databases were searched from their inception. The search was conducted June 28th, 2020 and included the following databases: EMBASE, Medline, CINAHL, and SPORTdiscus (see Appendix 2 for the detailed search strategy). The electronic search strategy was created by an experienced information services librarian using the following combination of search terms and identified keywords relevant to the main subject of the scoping review: aerobic exercise, AE, acute aerobic exercise, single-session, transcranial magnetic stimulation, single-pulse TMS, motor evoked potential, corticospinal excitability, CS excitability.

The search strategy underwent peer review by a second information services librarian using PRESS (Peer Review of Electronic Search Strategies; Appendix 1; McGowan et al., 2016) prior to it being executed. Peer review resulted in the addition of some keywords related to the research question which increased the number of studies resulting from the database search (Appendix 2). Design and execution of the scoping review was guided by the Preferred Reporting Items for Systematic Reviews and Metanalyses guidelines for scoping reviews (PRISMA-ScR; Appendix 3; Tricco et al., 2018) including reporting on search strategy, inclusion/ exclusion criteria, screening strategy, and data extraction and synthesis.

3.2 Eligibility Criteria

The retrieved articles were assessed for inclusion according to the relevance of the content to the aim of the scoping review. The inclusion criteria were as follows: (1) study population includes healthy adult participants, or individuals who have experienced a stroke; studies with mixed populations (i.e., both healthy individuals and those who experienced a stroke) were included if available; (2) age 18 or older; (3) all study designs were included; (4) reported using single-pulse TMS to measure corticospinal excitability pre and post a bout of AE; (5) articles were included if there was an acute bout of AE done with a modality of exercise (e.g. cycling, treadmill, walking, and running). Studies not meeting the above criteria were excluded or if they (1) were not written in the English language; (2) were review papers; or (5) did not include human participants (i.e., animal studies).

3.3 Screening Strategy

Upon completion of the electronic database search for the relevant literature results were uploaded to Covidence. Duplicate results were identified and removed via Covidence, followed by screening which consisted of two phases, followed by a data extraction process. The first and second phases had specific inclusion and exclusion criteria. In the first phase, article titles and abstracts were screened by two independent reviewers with the goal of reducing the number of articles to undergo full text screening in phase 2 and ensure those that do undergo full text screening are relevant to the objective of the scoping review. Specific inclusion criteria for phase 1 included: (1) use of TMS for the measurement of cortical or corticospinal excitability; and (2) an aerobic exercise intervention. Conflicts between the two independent reviewers were resolved by a third reviewer. Articles meeting

phase 1 criteria were moved on to phase 2 review. In phase 2, the list of articles was imported from Covidence into Endnote X7®. Full text of each study was obtained using Endnote X7 ® "find full text" search tool. If the full text was not found using this method, it was obtained through the Dalhousie University Library database. As in the first phase, two independent reviewers screened the full text. If conflicts resulted following screening, the third reviewer assessed the articles to resolve the conflicts. To determine the eligibility of the studies in this phase, reviewers used the following criteria: (1) age 18 years or older; (2) included healthy individuals or individuals who had experienced a stroke, or both; (3) application of single-pulse TMS to assess corticospinal excitability by using one of the following measurement: stimulus-response (S-R) curve, input-output curve, single MEPs (including MEPs obtained at a fixed intensity of RMT e.g. 120% of RMT); and (4) included a single session of AE of low, moderate, or high intensity using either cycling, running, or a treadmill). Studies were excluded for the following reasons: (1) if the full text was not available; (2) if the study involved an anerobic exercise intervention (i.e., short duration of high intensity), or studies involving interval training or strength training (e.g., sprints, weightlifting, or isometric exercise). Articles remaining following phase 2 moved onto data extraction (described below), which involved extraction of data and entry into a custom form to summarize the results from the relevant studies to address the main objective of the present scoping review.

3.4 Data Extraction and Synthesis

Data from studies meeting the inclusion criteria and which passed through phase 2 screening were extracted into several categories by a single reviewer using a custom data extraction form created in Microsoft Excel® (see Appendix 4). A data extraction risk of

bias assessment checklist tool (Critical Appraisal Skills Programme CASP; Appendix 5(Critical Appraisal Skills Programme (CASP) UK, 2018) was used before data extraction was performed. First, information related to the study such as author, year, and country of publication were extracted. Second, demographic information including participants' sex, age, and health condition (healthy/stroke) were extracted to facilitate identification of any effect of these factors on the study outcome. If the participants had stroke, further information was extracted including lesion side, limb affected, and time since stroke. Third, types of questionnaires used in the studies (e.g., to assess their ability to undergo TMS, physical activity level, or suitability to perform exercise program). Fourth, information related to the experimental protocol was identified extracted, including presence of a graded maximal exercise test (GXT); what assessment of excitability was performed (e.g., corticospinal excitability/spinal excitability, or both); the modality used (e.g., single pulse TMS, percutaneous electrical stimulation); and muscle group tested (e.g., exercised/non-exercised muscle, upper or lower limbs). Fifth, data related to the intervention including the modality of exercise, intensity, duration (dose) was extracted. Lastly, the outcome measures were extracted including corticospinal excitability changes post AE (i.e., stimulus-response (S-R) curve, an input-output curve, single motor evoked potential (MEPs), mean MEP, or fixed intensity of RMT (e.g., 120% of RMT, or adjusted the stimulation intensity to evoke a certain MEP amplitude; e.g., 1 mV), and a secondary outcome which is the spinal excitability changes post AE measured by H-reflex amplitudes, M-max/H-reflex recruitment curve measurement, stretch reflex, or late responses.

After extracting all the data from the studies in the data extraction step, the effect of AE on corticospinal excitability mapped and compared across the pooled studies for the

scoping review. Factors of AE such as intensity, duration, and modality were compared to investigate the effect of each factor on the corticospinal excitability changes.

CHAPTER 4: RESULTS

4.1 Selection of Studies and Sources

The comprehensive search of the 4 electronic databases resulted in 489 articles being identified; 206 of these 489 articles were removed as they were duplicates, leaving 283 articles for phase 1 screening. Following review of titles and abstracts in phase 1 screening, 239 articles were excluded, leaving 44 articles for full text screening in phase 2. Following review of the full text, 27 articles were excluded leaving 17 that met the eligibility criteria and were included in the present scoping review. A summary of the screening process is shown in Figure 9. Following assessment for risk of bias (via the CASP), all the included studies were found to report valid results and were pertinent to the scoping review research question. CASP checklist results are summarized in Appendix 6A and 6B.

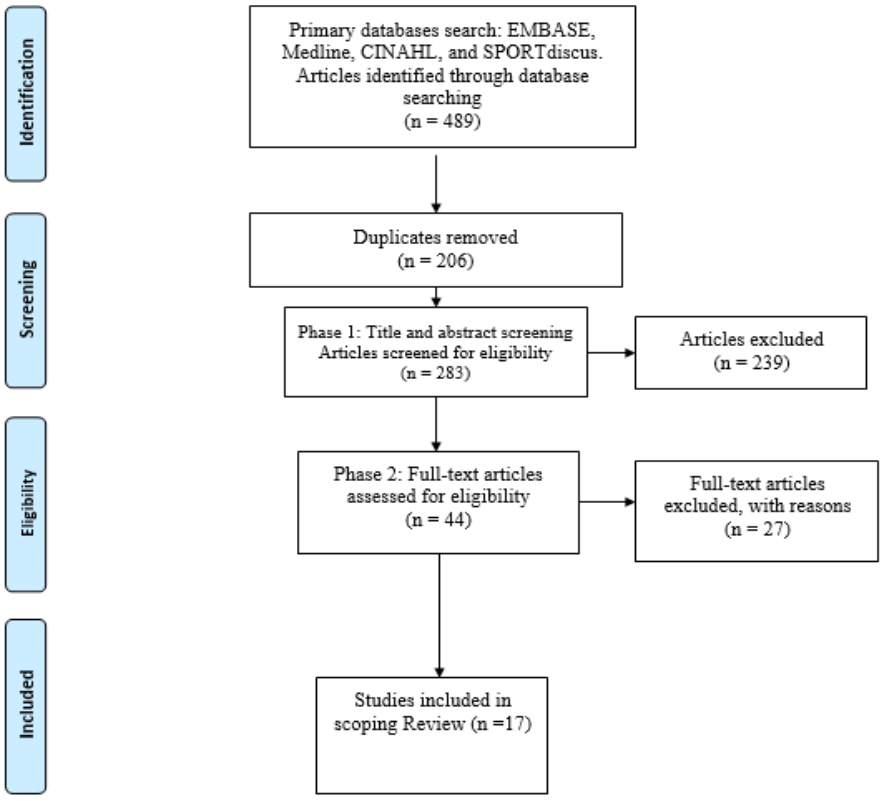

Figure 9. PRISMA flow diagram summarizing each stage of the search and screening process.

4.2 Study Characteristics

Characteristics relating to the population, methodology and interventions from the included studies are described below and summarized in Tables 1 through 4. In detailing our results, 7 out of 17 studies have several (1 to 4) experimental conditions. Those experiments have been labeled by letters next to the study number indicating them. As a result, we had a total of 28 separate experiments in the 17 studies included in the review. Details are presented in Table 1.

4.2.1 Population Characteristics

As indicated above, 17 studies met the eligibility criteria and were included in the current review. Across these 17 studies a total of 427 (53% females, 47% males) participants were included, with an average age of 29.1 years (SD ±12.2). Fourteen studies included healthy participants while three studies recruited stroke survivors; no studies examined both populations. For the three studies that included survivors of stroke, the average time since stroke was 24.7 months (range 6.5 months – 3.5 years). The majority of the studies used some form of screening to evaluate the participants. Twelve studies reported use of a TMS screening tool, while 9 of the 17 studies used some form of screening to determine suitability to perform exercise. Of these, 5 studies assessed the participants' suitability to perform exercise via the Physical Activity Readiness Questionnaire (PAR-Q), while 4 studies used the Sports Medicine Australia questionnaire (SMA-Q), an alternative questionnaire form. Also, ten studies evaluated the participants physical activity using the International Physical Activity Questionnaire (IPAQ), and 1 study used another variant of this (New Zealand Physical Activity Questionnaire; NZ-PAQ;). The population characteristics and questionnaire types are summarized in Tables 1 and 2.

4.2.2 Intervention Characteristics

Across the included studies the characteristics of the AE intervention differed. The characteristics that differed included intensity (i.e., low, moderate, and high), which was prescribed using various means including age predicted HRmax, HRR, rate of perceived exertion (RPE), and VO_2 peak, duration (range between 5 and 30 min) with a brief duration of warm-up and cooldown, and modality (cycling and treadmill). Before the actual intervention session, 6 of the 17 studies performed a GXT or variant (e.g., VO_2 peak test,

or aerobic incremental treadmill running test) to determine the participants' fitness level and the AE intensity for the subsequent AE sessions. Related to intensity level as shown in Table 3 below, nine of the 28 experiments performed low intensity AE, one performed low to moderate intensity AE, 14 performed AE at a moderate intensity, one of the experiments performed AE at a moderate to high intensity, and finally three studies performed AE at a high intensity. Related to the modality of AE, 13 of the 17 studies used cycling (recumbent ergometer, and upright stationary ergometer), with the remaining 4 studies using a treadmill. As noted above, the duration of the AE sessions also varied across the included studies. In one experiment the session of AE was completed in 5 min, whereas in another the AE was performed for 10 min. Two experiments had 15 min sessions, and 10 experiments conducted a 20 min session. Thirty minutes of AE was performed in 14 experiments. In relation to our study objective of examining the impact of AE on corticospinal excitability, all the 17 studies included assessed corticospinal excitability; 15 of the 17 assessed corticospinal excitability only, while the remaining 2 studies assessed both corticospinal and spinal level excitability. Out of 28 experiments within the studies, the corticospinal excitability changes were obtained in 25 experiments: 20 from non-exercised (upper limb) muscles, and 5 from the exercised (lower limb) muscles. On the other hand, in the 3 remaining experiments that measured the spinal excitability, one experiment obtained the spinal level excitability from the exercised (lower limb) muscle, while two other experiments obtained spinal excitability changes from the non-exercised (upper limb) muscles.

Table 1. Population characteristics of the studies included in the review.

Study No.	Author(s)	Year	No. of participants	Sex		Age	Study Indivisuals		Stroke		
				M	F	Mean	Healthy	Stroke	Lesion side	limbs affected	Time since stroke (m)
1	Singh	2014	12	7	5	28	Y				
2A	McDonnell	2013	25	9	16	27.8	Y				
2B	McDonnell	2013	25	9	16	27.8	Y				
3	Mooney	2016	10	7	3	23	Y				
4A	Garnier	2017	12	N/A	N/A	25	Y				
4B	Garnier	2017	12	N/A	N/A	25	Y				
5	Elsayes	2019	34	17	17	21	Y				
6A	Smith	2014	9	5	4	31.1	Y				
6B	Smith	2014	9	5	4	31.1	Y				
7	Lulic	2017	14	5	9	22.1	Y/High PA				
7	Lulic	2017	14	6	8	20.6	Y/low PA				
8	Morris	2020	14	5	9	26	Y				
9	Smith	2018	18	9	9	25.5	Y				
10A	MacDonald	2019	15	7	8	26.9	Y				
10B	MacDonald	2019	15	7	8	26.9	Y				
10C	MacDonald	2019	15	7	8	26.9	Y				
11A	Baltar	2018	12	3	9	23.5	Y				
11B	Baltar	2018	12	3	9	23.5	Y				
11C	Baltar	2018	12	3	9	23.5	Y				
12	Andrews	2020	20	9	11	35	Y				
13	Li	2019	13	11	2	65.77		Y	2 L / 11R	Unilateral	39.54
14	Boyne	2019	16	9	7	57.4		Y	N/A	Unilateral	6.5
15	Murdoch	2016	12	8	4	65.3		Y	6 L / 6 R	NA	28
16A	Neva	2017	10	N/A	N/A	26	Y				
16B	Neva	2017	10	N/A	N/A	26	Y				
17A	Yamazaki	2019	15	8	7	21.5	Y				
17B	Yamazaki	2019	14	7	7	21.1	Y				
17C	Yamazaki	2019	14	7	7	21.1	Y				
17D	Yamazaki	2019	14	7	7	21.1	Y				

Notes: N/A: Not Available. High physical activity level (High PA), low physical activity level (Low PA). Lesion side: left (L), and right (R). Time since stroke: months (m).

Table 2. Screening questionnaires used in included studies.

Study No.	Author(s)				
		TMS	PAR-Q	IPA-Q	Physical Activity Level (PAL)
1	Singh	Y	N/A	N/A	Moderately Active
2	McDonnell	*	SMA-Q	Y	High PAL were excluded
3	Mooney	Y	Y	(NZ-PAQ)	Moderate - High scores
4	Garnier	*	N/A	N/A	Regularly Active
5	Elsayes	Y	Y	Y	PAL scores not reported
6	Smith	Y	SMA-Q	Y	High PAL were excluded
7	Lulic	Y	Y	Y	High and Low
8	Morris	Y	Y	N/A	N/A
9	Smith	Y	SMA-Q	Y	High PAL were excluded
10	MacDonald	Y	Y	Y	Moderate - High
11	Baltar	*	N/A	Y	Irregularly Active
12	Andrews	Y	SMA-Q	Y	High scores
13	Li	Y	N/A	N/A	N/A
14	Boyne	*	N/A	N/A	N/A
15	Murdoch	Y	N/A	Y	Moderate- High scores
16	Neva	Y	N/A	Y	Moderate - High
17	Yamazaki	*	N/A	N/A	N/A

Notes: TMS screening; studies that checked for the contraindications for TMS using formal screening tool marked by (Y) while studies that did not report using a formal screening assessment are marked by an asterisk (*). Physical Activity Readiness Questionnaire (PAR-Q); Sports Medicine Australia questionnaire (SMA); International Physical Activity Questionnaire (IPAQ); and New Zealand Physical Activity Questionnaire (NZ-PAQ).

Table 3. Intervention characteristics across the included studies.

Study No.	Author(s)	Year	Intervention										
			TMS			GXT?	Modality	Intensity	Intensity Level		Duration	Warm-up	Cool-down
			Muscle	Muscle Tested	Limb Tested					ACSM*			
1	Singh	2014	ECR	Non-exercised	UL	No	Cycling	65-70% of age-predicted HRmax	Moderate	Moderate	20 min	N/A	N/A
2A	McDonnell	2013	FDI	Non-exercised	UL	No	Cycling	57% of age-predicted HRmax	Low	Low	30 min	N/A	N/A
2B	McDonnell	2013	FDI	Non-exercised	UL	No	Cycling	75% of of age-predicted HRmax	Moderate	Moderate	15 min	N/A	N/A
3	Mooney	2016	FPB	Non-exercised	UL	VO2 peak test	Cycling	60% of VO2 peak	Moderate	N/A	30 min	N/A	N/A
4A	Garnier	2017	APB	Non-exercised	UL	Max-AITRT	Treadmill	uphill +10 slope at 60% of HRmax	Moderate	Low	30 min	10 min	N/A
4B	Garnier	2017	APB	Non-exercised	UL	Max-AITRT	Treadmill	downhill -10 slope at 60% of HRmax	Moderate	Low	30 min	10 min	N/A
5	Elsayes	2019	FDI	Non-exercised	UL	VO2 peak test	Cycling	65-70% of HRmax	Moderate	Moderate	20 min	5 min	5 min
6A	Smith	2014	FDI	Non-exercised	UL	No	Cycling	40% of predicted HRR	Low- Moderate	Moderate	30 min	5 min	5 min
6B	Smith	2014	FDI	Non-exercised	UL	No	Cycling	80% of predicted HRR	Moderate- High	High	30 min	5 min	5 min
7	Lulic	2017	FDI	Non-exercised	UL	No	Cycling	50-70 % of age-predicted HRmax	Moderate	Moderate	20 mins	5 min	5 min
8	Morris	2020	FDI	Non-exercised	UL	No	Cycling	40% - 60% of HRR	Low	Moderate	30 min	5 min	2 min
9	Smith	2018	FDI	Non-exercised	UL	No	Cycling	80% of predicted HRR	High	High	30 min	5 min	N/A
10A	MacDonald	2019	ECR	Non-exercised	UL	Y	Cycling	30% of HRR	Low	Low	20 min	N/A	N/A
10B	MacDonald	2019	ECR	Non-exercised	UL	Y	Cycling	40% of HRR	Moderate	Moderate	20 min	N/A	N/A
10C	MacDonald	2019	ECR	Non-exercised	UL	Y	Cycling	50% of HRR	Moderate	Moderate	20 min	N/A	N/A
11A	Baltar	2018	TA	Exercised	LL	No	Treadmill	57-63% of age-predicted HRmax	Low	Low	30 min	N/A	N/A
11B	Baltar	2018	TA	Exercised	LL	No	Treadmill	64-76% of age-predicted HRmax	Moderate	Moderate	15 min	N/A	N/A
11C	Baltar	2018	TA	Exercised	LL	No	Treadmill	77-95% of age-predicted HRmax	High	High	10 min	N/A	N/A
12	Andrews	2020	FDI	Non-exercised	UL	No	Cycling	50% of HRR	Moderate	Moderate	20 min	2 min	2 min
13	Li	2019	ECR	Non-exercised	UL	No	Treadmill	70-85% of age-predicted HRmax	High	Moderate- High	5 min	N/A	N/A
								or RPE (13-15)					
14	Boyne	2019	VL	Exercised	LL	Y	Treadmill	45±5% of HRR	Moderate	Moderate	20 min	3 min	2 min
15	Murdoch	2016	FDI	Non-exercised	UL	No	Cycling	50 rpm / RPE (11-13)	Low	N/A	30 min	N/A	N/A
16A	Neva	2017	APB	Non-exercised	UL	No	Cycling	65-70%of age-predicted HRmax	Moderate	Moderate	20 min	5 min	N/A
16B	Neva	2017	APB	Non-exercised	UL	No	Cycling	65-70%of age-predicted HRmax	Moderate	Moderate	20 min	5 min	N/A
17A	Yamazaki	2019	FDI	Non-exercised	UL	VO2 peak test	Cycling	30 % of VO2 peak	Low	N/A	30 min	N/A	N/A
17B	Yamazaki	2019	TA	Exercised	LL	VO2 peak test	Cycling	30 % of VO2 peak	Low	N/A	30 min	N/A	N/A
17C	Yamazaki	2019	FDI	Non-exercised	UL	VO2 peak test	Cycling	30 % of VO2 peak	Low	N/A	30 min	N/A	N/A
17D	Yamazaki	2019	TA	Exercised	LL	VO2 peak test	Cycling	30 % of VO2 peak	Low	N/A	30 min	N/A	N/A

Notes: Muscles: Extensor Carpi Radialis (ECR); First Dorsal Interosseous (FDI); Flexor Policies Brevis (FPB); Abductor Policies Brevis (ABP); Tibialis Anterior (TA); and Vastus Lateralis (VL). Limb Tested: Upper Limb (UL), and Lower Limb (LL). Graded exercise: Maximal Graded Exercise Test (GXT), VO2 peak test, or Maximal aerobic incremental treadmill running test (Max-AITRT). Intensities: age-predicted maximum heart rate (HR_{max}); peak oxygen uptake (VO_2 peak); heart rate reserve (HRR); and rating of perceived exertion as modified Borg Scale (RPE). The American College of Sports Medicine (ACSM) (2018) guidelines for exercise testing and prescription defined low intensity as 57-63% of HR_{max} and 30-39% of HRR, moderate intensity as 64-76% of HR_{max} and 40-59% of HRR, and high intensity as 77-95% of HR_{max} and 60-89% of HRR.

Table 4. Excitability assessments across the included studies.

Study No.	Author(s)	Assessment		
		CSE	SE	both?
1	Singh	Y		
2	McDonnell	Y		
3	Mooney	Y		
4	Garnier	Y		
5	Elsayes	Y		
6	Smith	Y		
7	Lulic	Y		
8	Morris	Y		
9	Smith	Y		
10	MacDonald	Y		
11	Baltar	Y		
12	Andrews	Y		
13	Li	Y		
14	Boyne	Y		
15	Murdoch	Y		
16	Neva			Y
17	Yamazaki			Y

Notes: corticospinal excitability (CSE), and spinal excitability (SE).

4.3 Changes in Corticospinal Excitability

4.3.1 Changes in corticospinal excitability in healthy individuals' studies

Of the 22 experiments that examined corticospinal excitability in healthy individuals, 7 showed an enhancement of corticospinal excitability, while the remaining 15 did not (Table 5). Studies that showed an enhancement were distinguished by moderate intensities with variable duration of 15 to 30 min. For example, studies 5, 7, and 10B and C all featured AE interventions that had participants cycling at a moderate intensity (65-70% of HR_{max}, 50-70% of age predicted HR_{max}, and 40-50% of HRR, respectively) for a duration of 20 min. Their findings revealed an increase in corticospinal excitability (change in MEP amplitude via SR-curve). Study 5, which separated male and female participants to specifically examine the impact of the menstrual cycle, showed the increase in corticospinal excitability was similar among the female and male participants. In study 7, the increase in corticospinal excitability was specific to participants who were characterized as having a high level of physical activity compared to those with a low level of physical activity. In line with the results reported above for cycling-based AE, three out of 7 studies found that there was a modulation in corticospinal excitability following moderate intensity AE performed via treadmill. Particularly, experiments 4A and B showed that following uphill (4A) and downhill (4B) treadmill-based AE performed at a moderate intensity (60% of HR_{max}) for 30 min there was a significant increase in mean MEP amplitude post 30 min, although this increase was not seen post 5 min or post 15 min of AE. A similar finding of increasing corticospinal excitability (i.e., in the exercised muscle) was reported in expirement11B which also used treadmill-based AE albeit with a shorter

duration session (15 vs. 30 min) at an intensity which ranged between 64 and 76% of age-predicted HR_{max}.

Contrary to the above findings, 15 experiments showed that there was not a significant effect of the AE interventions on corticospinal excitability within the representation of the muscles involved (lower limb) and not involved (upper limb) in the AE. This finding was inclusive of studies that used cycling-based AE at low (2A, 10A, 17A, and 17B), low-moderate (6A), moderate (1, 2B, 3, 12, and 16A), and moderate-high (6B) intensity. Experiment 11A also reported that treadmill-based AE performed at a low intensity did not have a significant effect on corticospinal excitability in the exercised muscle. The specific exercise intensities for each of these studies are listed in Table 3 above; for example, experiment 10A had participants exercise at a low intensity (30% of HRR), while experiment 6A had participants exercise at a low-moderate intensity (40% of HRR), and in study 3 participants cycled at a moderate intensity (60% of VO_2 peak). An example of moderate to high intensity was observed in experiment 6B where participants cycled at 80% of HRR. One study (8) had a paradigm in which participants had prior exposure to cognitive tasks before and immediately after the AE intervention, with the TMS measurements being obtained after the cognitive assessment. In this particular study (8) participants performed low intensity cycling between 40 and 60% of their HRR. The result demonstrated that no significant change in MEP amplitudes was observed. High intensity cycling (80% of HRR) also did not result in a change in corticospinal excitability, as demonstrated in studies 6B and 9. High intensity AE performed via treadmill (77-95% of age-predicted HR_{max}) also did not drive an increase in corticospinal excitability – rather,

this experiment (11C) showed a decrease in corticospinal excitability in the exercised muscle.

Regardless of the exercise intensity, the duration of the AE varied considerably across the studies which showed no effect of AE on corticospinal excitability. For instance, in experiment 11C, participants performed the treadmill-based AE for 10 min at a high intensity (77-95% of age-predicted HR_{max}), while participants in experiment 2B cycled at a moderate intensity (75% of age-predicted HR_{max}) for 15 min. Studies 1, 10A ,12, and 16A had participants cycle for 20 min. Longer durations of AE was used in several studies; studies 2A, 3, 8 ,11A, 17A, and 17B had participants perform AE for 30 min, a similar duration to studies 6A, 6B, and 9 which included two consecutive blocks of 15 min each. No changes in corticospinal excitability or differences in MEPs was reached post a single session of lower limb AE.

Table 5. Changes in corticospinal excitability across the studies examining healthy participants.

Study No.	Changes in Corticospinal Excitability		
	↑	↓	–
1			–
2A			–
2B			–
3			–
4A	↑		
4B	↑		
5	↑		
6A			–
6B			–
7	↑		
8			–
9			–
10A			–
10B	↑		
10C	↑		
11A			–
11B	↑		
11C		↓	
12			–
16A			–
17A			–
17B			–

Notes: Green 'up' arrows represent an increase in CSE following a session of AE, while red 'down' arrows represent a decrease in CSE. The blue dash represents no change CSE post a session of AE.

4.3.2 Changes in corticospinal excitability in studies of stroke survivors

One of the three studies that included stroke survivors showed that AE resulted in a significant increase in corticospinal excitability (i.e., MEP amplitude) in the nonexercised muscle within the lesioned hemisphere of the brain following a 5 min session of high intensity (70-85% of age-predicted HRR) AE performed on a treadmill (study 13). In contrast, study 14, which had participants perform AE on a treadmill at a moderate intensity (45 ± 5% of HRR) for 20 min, did not show a change in corticospinal excitability in the lesioned hemisphere representation of the lower limb that was involved in the exercise (vastus lateralis muscle). The final study examining survivors of stroke used cycling (as opposed to a treadmill) at a low intensity (50 rpm with a reach of 11-13 level on Borg's scale) for a longer duration (30 min). The result of this study (15) aligned with that of study 14, reporting no change in corticospinal excitability in the non-exercised muscle within the affected hemisphere following the AE session. Table 6 summarizes the findings for studies examining survivors of stroke.

Table 6. Changes in corticospinal excitability across studies examining stroke survivors.

Study No.	Changes in Corticospinal Excitability		
	↑	↓	–
13	↑		
14			–
15			–

Notes: Green 'up' arrows represent an increase in CSE following a session of AE, while red 'down' arrows represent a decrease in CSE. The blue dash represents no change CSE post a session of AE.

4.4 Changes in the Excitability at Cortical vs. Spinal levels

Of the 17 studies, two studies (Studies 16 and 17) examined the effect of lower limb cycling exercise on changes in corticospinal and spinal excitability. In study 16, a bout of moderate intensity cycling (65-70% of age- predicted HR_{max}) for 20 min did not significantly influence change in corticospinal excitability post versus pre-exercise as assessed through a stimulus response curve (16A), or spinal excitability (16B), as assessed via the H-reflex and V-wave amplitudes, in the non-exercised muscle. This result was consistent with the findings of no increase in corticospinal or spinal level excitability observed in non-exercised muscles reported in study 17 experiments 17A and 17C, and in the exercised muscles in experiments 17B and 17D. However, study 17 had a comparably lower intensity (30% of VO_2 peak), longer duration (30min), and used a different approach to assess the changes in corticospinal excitability, with the stimulator fixed at an intensity to evoke an MEP of 1 mV in experiment (17A), and single-pulse TMS at 120% RMT in study (17B). Further, spinal excitability was assessed via the late response (i.e., the F-wave; experiment 17 C and D) across several time points post the AE session (post 5, 20, 40, and 60 min). The findings showed that there were no significant changes in corticospinal excitability based on the amplitude of the MEPs elicited from the upper-limb of the non-exercised muscle (17A), or lower-limb exercised muscle (17B), and no significant changes in spinal excitability based on the amplitude of the F-wave obtained from either the non-exercised muscle (17C), or exercised muscle (17D) at all time points after the exercise session. Table 7 below represents the cortical vs. spinal level changes obtained across these studies.

Table 7. Changes in corticospinal excitability and spinal excitability.

Study No.	Changes in Corticospinal Excitability			Changes in Spinal Excitability		
	↑	↓	–	↑	↓	–
16A			–			
16B						–
17A			–			
17B			–			
17C						–
17D						–

Notes: Green 'up' arrows represent an increase in CSE following a session of AE, while red 'down' arrows represent a decrease in CSE. The blue dash represents no change CSE post a session of AE.

CHAPTER 5: DISCUSSION

5.1 Changes in Corticospinal Excitability

The objective of this scoping review was to investigate the available evidence on corticospinal excitability changes resulting from AE among healthy individuals as well as individuals who have experienced a stroke. Specifically, the review aimed to 1) explore whether an acute bout of AE drives an increase in corticospinal excitability, and if so, what factors influence this; and 2) explore whether increases in corticospinal excitability in response to an acute bout of AE occur at the cortical or spinal level, or both. Addressing this objective is of importance given that neural plasticity is facilitated when the brain is in an excitable state; thus, understanding how AE impacts on the excitability of the brain has implications for many disciplines where learning or re-learning motor skills is required. The results suggest that there is considerable variability in the effect of an acute bout of AE on corticospinal excitability, both in healthy individuals as well as individuals' post-stroke. The intensity, duration and modality of the AE all appear to influence the effect of an acute bout of AE on corticospinal excitability; however, variability in these factors across the included studies limits the ability to fully understand their impact. Given that few studies compared changes in excitability at both the cortical and spinal levels, we were limited in our ability to address the second aim.

Of the 22 experiments that investigated a change in corticospinal excitability after AE in healthy individuals, seven reported an increase in corticospinal excitability post an exercise session, while the other 15 did not report an increase in corticospinal excitability (see Table 5). Additionally, only one of the three studies that examined individuals post-stroke showed an enhancement of corticospinal excitability after the bout of AE (see Table

6). The variability associated with the prescription and delivery of the acute bout of AE applied across the studies (see Table 3) may have contributed to the discrepancy in the results which demonstrated that there is either an increase, decrease, or no change in corticospinal excitability or spinal level excitability after a session of AE across populations of healthy individuals or those who have experienced a stroke who were included in the studies reviewed. Notable among the factors that may have resulted in this discrepancy include the intensity, duration, and modality of the AE.

5.1.1 The effect of AE intensity

While there are a number of factors that likely impact on the effect of AE on corticospinal excitability, the intensity of the AE appears to contribute substantially. Across studies, it was found that neither low or high intensity AE resulted in an increase in corticospinal excitability, regardless of modality (cycling or treadmill), duration (short or long) or whether the excitability measures were obtained from a muscle that was directly involved in the exercise (i.e., the lower limb) or not (i.e., the upper limb). The majority of the studies that reported either a decrease or no change in corticospinal excitability (assessed via MEP amplitude) were those which used low (defined as 30% or 40-60% of HRR, 30% of peak VO_2, 57-63% of age-predicted HR_{max}) or high (defined as 77-95% of age-predicted HR_{max} and 80% of HRR) intensity AE. For low intensity AE, there were several studies that did not demonstrate an effect: MacDonald et al. (2019) (experiment 10A) had participants perform a single, 20 min session of AE at a low intensity (30% of HRR, equivalent to approximately 57% of age-predicted HR_{max}), showing there was no change in corticospinal excitability post the low intensity exercise session. In congruence with this study, McDonnell et al. (2013) (experiment 2A) showed that cycling at the same

intensity (i.e., low; 57% of age predicted HR_{max}) also demonstrated no change in corticospinal excitability. A similar result was reported in Yamazaki et al. (2019) study (17A and B) where they utilized low intensity AE (30% of VO_2 peak). Baltar et al. (2018) (experiment 11A) found the same result while applying the same session length (30 min) and intensity (57-63% of age predicted HR_{max}). A different paradigm conducted in one study, Morris et al. (2020) (study 8), included exposing the participants to three cognitive tasks before and after low intensity AE (40% - 60% of HRR), with TMS measures taken following completion of the cognitive tasks. They found that the amplitude of the MEPs obtained from an intrinsic hand muscle at a fixed intensity of stimulator output were not changed. This is likely because the time interval between the pre-exercise TMS and the post-exercise TMS assessment was approximately 3 hours, which may have resulted in a degraded effect of AE on corticospinal excitability. Taken together, the lack of a change in corticospinal excitability after low intensity AE may be attributed to the fact that this intensity is not sufficient to trigger changes in neural elements (e.g., neuromodulatory agents among others, discussed in detail below) with the representations of either the exercised or the non-exercised muscle regardless of duration or modality of exercise used. Like the findings for low intensity AE, the results of the two high intensity AE studies, and one moderate-high intensity study, also showed no change in corticospinal excitability, regardless of exercise modality or duration. For example, 10 min of treadmill-based AE at (77-95% of age-predicted HR_{max}) decreased corticospinal excitability and similarly, cycling at a high intensity (80% of HRR) for 30 min (two blocks of 15 min) did not change corticospinal excitability as assessed by the S-R curve and single MEPs either immediately following the session (studies 6B, and 9) or post 15 min (experiment 6B). Of the 14

experiments that looked at moderate intensity AE, there were conflicting results where some experiments showed an increase in corticospinal excitability, and others did not (see Table 5). While there is consistency in the intensity used across the studies (in the range of 64-76% of age-predicted HR_{max}, 60% of VO_2 peak, and 40-50% of HRR), other factors such as duration and modality of exercise varied. These factors may have an impact on corticospinal excitability and are discussed in the sections below.

5.1.2 The Effect of AE Duration

The pattern of changes in corticospinal excitability following an acute bout of moderate intensity AE was inconsistent across the included studies. The inconsistency in the findings may have been further increased by the different durations of AE used among the studies. Fourteen of the 28 experiments included a bout of moderate intensity AE (in the range of 64-76% of age predicted HR_{max}, 60% of VO_2 peak, and 40-50% of HRR, as detailed above) with various session lengths. For example, cycling at a moderate intensity (75% of age predicted HR_{max}) for a shorter duration (15 min) did not show an effect on corticospinal excitability. This extends to the findings of Neva et al. (2017) and Andrews et al. (2020), with the latter study reporting no change in corticospinal excitability after increasing the duration of the cycling to 20 min. While these studies did not observe changes in excitability, four other studies (5, 7, 10B, C) which performed the same intensity and duration of exercise (20 min) did report an increase in corticospinal excitability as assessed by the S-R curve. Also, with a slightly shorter duration of 15 min, experiment 11B (64-76% of age-predicted HR_{max}) reported an increase in corticospinal excitability. Interestingly, performing a longer duration of AE (30 min, as in Smith et al. (2014) (experiment 6A) at a low-moderate intensity (40% of predicted HRR), and Mooney et al.

(2016) (study 3) at a moderate intensity (60% of VO_2 peak) did not show an alternation in corticospinal excitability. Nonetheless, two other experiments reported that a single session of moderate intensity (60% of HR_{max}) AE of 30 min increased corticospinal excitability (experiments 4A & B).

The optimal duration of AE that would induce an increase in corticospinal excitability is yet to be determined. A previous review conducted by El-Sayes et al. (2019) suggested that a single session of AE with a length of 20 min is adequate to drive neuroplasticity. As has been shown by Schmidt-Kassow and colleagues in (2012), the maximum levels of serum BDNF concentration is reached following 20 min of AE, while after 30 min of AE no further increase was detected. In line with these suggestions, the results of the studies in this scoping review showed that similar session durations led to different findings in modulating corticospinal excitability. Studies that have reported an increase in corticospinal excitability performed exercise sessions for the suggested duration of 20-30 min with the exception of one study that performed AE for 15 min. Together, one interpretation for the inconsistency in these findings is that an AE session for any specific duration may only induce corticospinal excitability when other known and unknown factors are optimal for the brain excitability to happen. Known factors include the intensity and the modality of the AE, as well as other methodological considerations including participant characteristics (e.g., biological sex, physical activity level and fitness level).

5.1.3 The Effect of AE Modality and Muscle Tested

Amongst the studies, corticospinal excitability following a cycling-based session of AE was increased as assessed in the non-exercised upper limb muscle (studies 5, 7, and 10), but was found to be unchanged in others (studies 1, 2, and 6); a similar finding of no

change in corticospinal excitability was found for study 17B which assessed the lower limb exercised muscle. All studies that used moderate intensity treadmill-based AE (4A, B and 11B) reported an increase in corticospinal excitability within either the non-exercised or exercised muscle. This finding suggests that the modality of AE (cycling vs. treadmill) may have an impact on whether or not the exercise is effective in increasing corticospinal excitability. Exercise performed on a cycle ergometer allows the movement of the upper body to be reduced, and permits the exercise to be non-weight-bearing (American College of Sports Medicine, 2000). Conversely, exercise performed on a treadmill enhances the activity of the whole body (musculoskeletal system), increasing the physiologic stress and workload (American College of Sports Medicine, 2000). It has been demonstrated that during locomotor exercise (i.e., via a treadmill), the cardiovascular and metabolic demands are increased (Sidhu et al., 2013). While our findings suggest that AE performed via a treadmill may be more effective in increasing corticospinal excitability, additional research is required to compare the effect of the modality of AE on corticospinal excitability, with a specific focus on controlling for intensity and duration to isolate the effect of modality.

5.1.4 Methodological Considerations

As indicated previously, the method of determining the intensity of the AE used in each study was provided in Table 3. Based on Table 3, it is clear that there were differences in the way in which the intensity of the AE across studies was determined, and this may be associated with the variability in the findings across studies. For instance, the GXT is recognized as a gold standard process for determining maximum values of HR, or power output, as well as to determine the maximal oxygen consumption (VO_{2max}) (Albouaini et al., 2007) and for subsequently determining exercise prescription, exertion during exercise,

or cardiovascular compliance to exercise testing (Azevedo et al., 2011; Bickelmann et al.,1963). In MacDonald et al. (2019) (study 10), a GXT was performed prior to the experimental session (during their familiarization session) and the intensity of AE performed in subsequent sessions determined based on the outcome of this GXT. This process, however, was not always performed across all of the included studies. Many studies used an alternative approach to estimate the HR_{max}, including estimation based on age using the equation [HR_{max} = 220-age] (Shookster, Lindsey, Cortes, & Martin, 2020). While common, it has been documented that there is a limited predictive accuracy of using this approach to determine the predicted maximum heart rate (Cleary et al., 2011; Nikolaidis et al., 2014; Robergs & Landwehr, 2002; Verschuren et al., 2011; Whaley et al., 1992; Whyte et al., 2008). As shown in Singh et al. (2014) (study 1) and Lulic et al. (2017) (study 7) in which this equation was used, it could be possible that some of the participants did not actually perform the AE at the intended moderate intensity (i.e., they may have been below or above the intended intensity). This example illustrates the possibility of why we observed variable findings of no change in corticospinal excitability or an increase in corticospinal excitability despite the study using a similar intensity and duration. This could be explained by what is suggested in the evidence: that prediction of HR_{max} from a given age may not give a valid measure to use in exercise prediction for determining the exact exercise intensity (Sarzynski et al., 2013). In a similar vein, use of the Karvonen formula (HR_{max}−resting HR) ∗ intensity [0.4−0.6]) + resting HR) as seen in Morris et. al., 2020 (study 8), or use of other approaches such as the equation (180 − RHR) × (intensity%) + RHR) in Smith et al. (2014) (study 6) and Smith et al. (2018) (study 9) may underestimate or overestimate the intensity of AE (Ignaszewski et al., 2017). Lastly, according to

evidence, HR can naturally fluctuate and may not be a stable measure even in healthy people (Sayers,1973); thus, prescribing AE based on HR may result in variability in the actual intensity of the AE being performed. An alternative to this approach is to use consistent values such as a percentage of maximal power output for exercise prescription, as working at a percentage of maximum power output is consistent from day to day unlike HR.

In addition to the method of determining AE intensity, there are other methodological and technical considerations which may influence the outcomes, including the time of data collection after the AE intervention to detect changes in corticospinal excitability. As has been shown in previous work following a single session of electrical stimulation either combined with voluntary movement or not, the increase of corticospinal excitability can be measured after at least 30 min of the AE session and continue to be detected 150 min later (Fraser et al., 2002; Khaslavskaia et al., 2002; Charlton et al., 2003; Kido-Thompson and Stein ,2004; Khaslavskaia and Sinkjaer, 2005). In contrast with this work, in the TMS studies included here, there was considerable variability in the time point(s) at which corticospinal excitability was assessed, with many performing assessments early after the AE intervention. For example, Garnier et al. (2017) (study 4) performed the TMS measurements at different time points including 30 min post exercise cessation, and they found an increase in corticospinal excitability only after 30 min has passed since the AE session, whereas Singh and colleagues did not find changes in corticospinal excitability either immediately post or 30 min post AE.

5.1.5 The Effect of Participant Variability on corticospinal excitability

Besides the factors associated with AE that were discussed above, it has been found that other factors can have an influence on the modulating effect of AE on corticospinal excitability. Indeed, there are questions regarding the effect of hormonal fluctuations and biological sex on corticospinal excitability as suggested by (Smith et al., 2002). In this regard, one study (El-Sayes et al., 2019) examined the effect of the fluctuation of ovarian hormones in females throughout the menstrual cycle by examining CSE in a group of female participations against a matched group of male participants. The study found that there was no difference between the two groups in regard to the increase in corticospinal excitability following a bout of moderate intensity cycling exercise. The authors concluded that the fluctuation of ovarian hormone levels had no effect on CSE after a short bout of acute AE.

The behavior of the corticospinal excitability response appears to be somewhat dependent on the level of participant's physical activity (Suruagy et al., 2017). It has been shown that regularly active individuals compared to sedentary individuals have a greater response to AE, in that the AE induces a larger increase in corticospinal excitability (Cirillo et al., 2009). Four experiments reported a positive relationship between physical activity level (high-moderate), or cardiorespiratory fitness level (fair or higher) with an increase in corticospinal excitability (Lulic et al., 2017, study 7; MacDonald et al., 2019, study 10B and C; and El-Sayes et al., 2019, study 5). Typically, the means of assessing physical activity level is through participant self-report. For instance, the I-PAQ is an assessment tool of physical activity level based on the time spent in physical activity domains per week (Straatmann, dos Santos, Palma, & da Veiga, 2014). According to I-PAQ guidelines (2005), participants can be divided based on their physical activity levels into three

categories; participants who have scores at a minimum of 3000 MET-min/week are considered as having a high physical activity level, where participants with scores at a minimum of 600 MET-min/week are considered moderate, while low physical activity level is determined if participants did not meet the cut-off for either of the other two categories (i.e., high or moderate). A concern regarding the measure of an individual's physical activity level by this means is that these approaches are based on self-report. In a review done by Prince and colleagues (2008), they showed that self-report questionnaires can lead to the under or overestimation of the individual's actual physical activity level. This may create issues associated with bias, where participants responses do not accurately reflect their actual physical activity levels and in-turn impact on experimental screening procedures – e.g., a person with lower levels of physical activity report higher levels on the I-PAQ, and in-turn are included in the high, as opposed to low, physical activity group in a research study (Prince et al., 2008). For example, Lulic and colleagues (2017) showed an increase in corticospinal excitability within high physical activity participants who accumulated more than 3000 MET-min/ week as opposed to low physical activity participants with less than 3000 MET-min/week as assessed via the I-PAQ. In their study, participants were grouped and enrolled in these two categories (high vs. low physical activity), but any participant who was below the cutoff for high physical activity (3000 MET-min/week) were considered to have a low physical activity level. This approach to group assignment resulted in the low physical activity level group actually being a mixed group of moderate and low physical activity individuals. However, it is not clear if the individual's physical activity level impacts the response of corticospinal excitability increase. In contrast to the findings of Lulic and colleagues, Neva et al. (2017) (study16),

Singh et al. (2014) (study 1) and Andrews et al. (2020) (study 12) enrolled a moderate-high physical activity population, and no changes in corticospinal excitability were detected. Unlike Lulic however, in Singh et al. (2014) (study 1), it was not indicated that their participants were screened for their physical activity level (moderate physical activity level) using a formal tool (e.g., I-PAQ). That there is variability in corticospinal responses is clear from Baltar, et al. (2018) (study 11B), which showed that participants who only irregularly engaged in physical activity (as assessed via I-PAQ) had increased corticospinal excitability 10 min post moderate intensity (walking) on a treadmill. While not necessarily reflective of physical activity level, other work has shown a participant's aerobic fitness (as assessed via VO_{2max}) was not related to the magnitude of change in corticospinal excitability observed after a single bout of AE at moderate intensity (50% of HRR) for 20 min (MacDonald et al., 2019). The variability in the findings related to participant's physical activity level warrant additional research to explore this factor and its effect on changes in corticospinal excitability.

Other factors also need to be considered as they have the potential to affect corticospinal excitability and relate to the participants performing the AE session. These include caffeine intake and exercise. Performing exercise on the day of testing, or ingestion of caffeine (via any caffeinated drink) shortly before performing the AE intervention and TMS assessments may have an adverse implication on the findings. While some studies controlled these factors and informed participants to avoid ingesting caffeine or heavy meals, other did not. For instance, the instruction to refrain from performing any exercise on the day of testing is a recommendation from the American College of Sports Medicine (ACSM) (Pescatello, 2014). Additionally, previous work has shown other variables such

as the participant's motivation to participate, sleep quality, duration of sleep or the level of tiredness may influence cortical excitability (Oliviero et al., 2006; Perciavalle et al., 2010). All of those factors indicated previously may contribute to the variability of findings amongst studies that have similar exercise protocols with different results.

Taking together, the complexity of the AE parameters and inter-variability characteristics across the studies make it unclear to us which are the optimal factors that have the most impact on increasing corticospinal excitability.

5.2 Changes in Spinal Excitability

As indicated above, AE can have a significant effect on corticospinal excitability, but it is not clear if the excitability changes occur at the cortical or spinal level. The two studies (16 and 17) that examined the effect of AE on spinal level showed that no change in spinal excitability occurred post AE despite the variation in the intervention parameters, (i.e., intensity and duration of AE), the muscle tested, and the means of measuring the changes. It is important to note, however, that given the low number of studies, the ability to recognize patterns in the data related to spinal level excitability and the impact of AE are limited.

5.2.1 Intensity of AE on spinal excitability

The included studies suggest that AE at either low or moderate intensity (30% of VO_2 peak, or 65-70% of age-predicted HR_{max}) does not result in a change in spinal-level excitability following a session of cycling-based AE (Yamazaki et al., 2019; Neva et al., 2017). This finding may be related to the conclusion above that low intensity AE is not sufficient to trigger a change in excitability of the spinal motor neurons or that spinal level excitability does not change following single session of AE regardless of the intensity or

duration of the exercise. While the moderate intensity study also did not result in a change in spinal-level excitability, it is difficult to draw any conclusions related to the finding given that only a single study was included.

5.2.2 Duration of AE on spinal excitability

In the two studies that were included, the duration of the AE did not appear to affect spinal level excitability. In Yamazaki et al. (2019) (study 17), cycling for 30 min (30 % of VO_2 peak,) did not modulate spinal level excitability. Moreover, Neva et al. (2017) (study 16) reported similar results after 20 min of cycling-based AE (65-70% of age-predicted HR_{max}). Overall, there is still no extensive work and knowledge regarding whether the effect of aerobic exercise mediates a change at cortex or spinal level, or at both sites.

5.3 Changes in Corticospinal Excitability Among Individuals Post-stroke

Previously, it was shown that a single bout of AE can induce a change in corticospinal excitability within healthy individuals following moderate intensity AE, however, we note the variability of this finding. As indicated previously, a secondary aim of this scoping review was to review the available evidence of the effect of a single session of AE on corticospinal excitability within a population of stroke survivors. In stroke, engaging participants in a session of exercise prior to their rehabilitation program, or motor skill training can alter the state of excitability of the pools of interneurons to be more responsive to rehabilitation strategies (Singh et al., 2014); in other words, this may prime the motor system for learning and relearning of motor skills (Statton et al., 2015; Li et al., 2019). In this scoping review, three studies (13, 14 and 15) aimed to determine the effect of AE on corticospinal excitability in participants who had experienced a stroke. While these studies had several similarities, including the mean age of participants, assessment of

the lesioned side, and the time since stroke (< 6 months), there were notable discrepancies between the findings of these studies that may relate to the exercise intensity, duration, or the muscle tested.

5.3.1 The effect of AE Intensity

As discussed above and proposed by Boyne and colleagues (2019), the intensity of the exercise is a key mediator that can influence the effects of priming via AE. As summarized in Table 3, low intensity AE (defined as reaching an RPE between 11-13), and moderate intensity AE (defined as 45 ±5% of HRR) did not induce changes in corticospinal excitability in the stroke affected brain, while high intensity (defined as 70-85% of age-predicted HR_{max}) did. Li et al. (2019) (study 13) demonstrated that high intensity AE increased corticospinal excitability within the lesioned hemisphere; however, it did not show the same effect on the non-lesioned hemisphere (Figure 10). The suggestion of this finding is that high, but not low or moderate intensity AE can drive an increase in corticospinal excitability; however, the very limited number of studies should be considered when interpreting this finding.

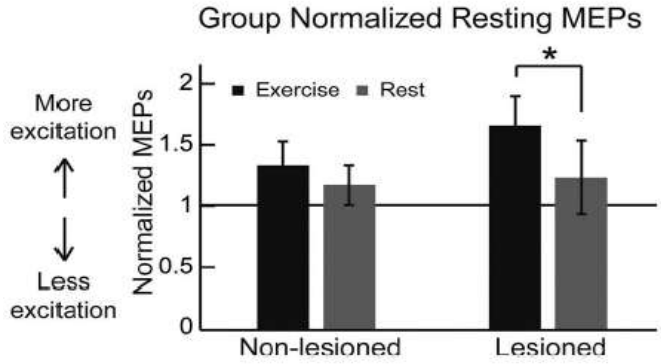

Figure 10. Changes in corticospinal excitability obtained from non-lesioned and lesioned hemispheres as assessed via normalized MEP amplitude (post/pre). Black bars represent the exercise sessions, while gray bars represent rest. There was a significant increase in corticospinal excitability within the lesioned hemisphere post AE ($p < .05$). Note, a value of 1 reflects there was no change in MEP amplitude after rest or exercise.

5.3.2 The effect of AE Modality and Duration

When comparing the 3 studies, there was a significant effect of an increase in corticospinal excitability as assessed by single MEPs (at fixed intensity of 120% RMT) after 5 min of fast walking on a treadmill (Li et al., 2019). However, no effect was observed after cycling for 30 min or exercising on a treadmill for 20 min as shown by Murdoch et al. (2016) (study 15) and Boyne et al. (2019) (study 14), respectively (see Table 3). The differences in the finding of those 3 studies may be attributable to the differences in the intensity, duration, or the modality of the exercise session used.

5.3.3 The effect of Muscle Tested

Functional improvement of the affected upper limb takes longer to recover, and recovery of the affected upper limb tends to be less complete (Schweighofer et al., 2009). Some studies suggest that AE increases corticospinal excitability broadly, meaning across

the population of neurons innervating the whole body (i.e., even for neurons that control muscles not directly involved in the exercise), and not limited to the muscles that are involved in a certain exercise (McDonnell et al., 2013). In support to this observation, the increase in the corticospinal excitability that was found in Li et al. (2019) study was measured in the non-exercised upper limb. This finding could provide a base for use of acute bout of lower limb exercise as a complimentary method in rehabilitation programs for stoke survivors.

Unfortunately, there were a limited number of studies available for inclusion in this review that examined the stroke population, which makes it difficult to draw any conclusions regarding the optimum parameters for AE that have the greatest influence on corticospinal excitability in this certain population.

5.4 The Effect of a Single Session of AE on Neurotransmitters and Neuromodulators

As discussed in the introduction, the increase in corticospinal excitability observed in the included studies is associated with the effect of the AE on neuromodulatory agents that impact excitability in the brain. The findings may be explained by evidence that a single session of AE can induce an increase in corticospinal excitability through modulating the aspects of communication between the synapses (Andrews et al., 2020). Along with that, (Smith et al., 2010) indicates that a single session of moderate intensity cycling has the ability to increase the global cerebral blood flow by 20%. Several TMS studies examining the primary motor cortex suggest that AE upregulates neurotrophic and growth factors in the brain (Cotman et al., 2007), and modulates the concentration of neurotransmitters in the brain (Lulic et al., 2017). These effects are involved in increasing the state of excitability of the neurons (Maddock et al., 2011; Maddock et al., 2016) by

reducing the effect of inhibitory neurotransmitters (i.e., GABA), and increasing the effect of the excitatory neurotransmitters (i.e., glutamate).

Similarly, it has been found that AE promotes an increase in the concentration of neurotransmitters including serotonin and dopamine, as well as norepinephrine, which in turn enhances the facilitation within motor cortex as indicated previously (El-Sayes et al., 2019; Singh & Staines, 2015). On the other hand, an increase in cortisol secretion, which can impede neuroplasticity (Sale et al., 2008; Rojas Vega et al., 2006), is found to be associated with moderate to high intensity AE. It has been demonstrated that cortisol secretion level increased by 10% immediately following 15 min of cycling at 75% of age predicted HR_{max} (McDonnell et al., 2013). Also, in a study done by Hill and colleagues (2008), it was shown that cortisol level was significantly changed after exercising for 30 min at either 60% or 80% of VO_{2max}, with corresponding increases in cortisol of 40 and 83%. This evidence further supports the findings of a decrease or no change in corticospinal excitability being observed following an acute bout of high intensity AE.

Related to participant characteristics, high levels of physical activity may influence the concentration of BDNF and its uptake by the neural cells (Cho et al., 2012; Currie et al., ,2009; Nofuji et al., 2012). There is growing evidence that the increase in the uptake of BDNF by the central nervous system may contribute to the increase in corticospinal excitability following a bout of moderate intensity exercise as indicated in the high physical activity group in Lulic et al. (2017) (Study 7). It has been shown that BDNF plays a role in decreasing the activity of GABAa receptors (Bruing et al., 2001), in-turn resulting in decreased inhibition of the post synaptic neuron and ultimately an increase in the influence

of incoming excitatory influences (Lessmann et al., 1994; Levine et al., 1995; Carmignoto et al., 1997).

5.5 Limitations and Future Directions

Although this scoping review highlights the effect of different intensities of AE on changes in corticospinal excitability, there were a number of limitations. One of the limitations was the variability in the definition of the AE intensities among the studies. Some studies classified the exercise intensity differently than the classifications outlined by the ASCM. The ACSM (2018) guidelines for exercise testing and prescription define low intensity as 57-63% of HR_{max} and 30-39% of HRR, moderate intensity as 64-76% of HR_{max} and 40-59% of HRR, and high intensity as 77-95% of HR_{max} and 60-89% of HRR. For instance, Garnier et al. (2017) (study 4) reported that their participants performed moderate intensity AE, which involved exercising at 60% of HR_{max}; however, based on the ACSM guidelines this intensity of exercise would be considered low. Another example of this was in Morris et al. (2020) (study 8), who reported participants as performing AE at a low intensity defined as 40% - 60% of HRR, which would actually be classified as being moderate intensity according to the ACSM guidelines. Moreover, some studies did not provide data related to the TMS measurements (e.g., MEP amplitude) and thus further interpretation of the data and findings could not be made (i.e., raw data was not available or reported). Also, although this scoping review involved a comprehensive search of four databases, the number of studies that matched the inclusion criteria was limited. As indicated by previous work, and in the current findings, that the intensity, duration, and mode of the AE may have a robust impact on modulating corticospinal excitability, future experimental studies or reviews are needed to better characterize the effective parameters

of single bout of AE on altering corticospinal excitability. Additional research examining different types of exercise (e.g., anaerobic exercise vs. aerobic, or continuous exercise vs. interval exercise), while controlling for factors such as intensity and duration, are needed. An additional limitation of the current work was limiting the search to only include measures associated with single-pulse TMS; inclusion of a broader range of measurements of corticospinal excitability and cortical excitability (including measures of inhibition and facilitation) would provide important insight related to the effect of AE on the brain. For instance, paired-pulse TMS can provide information related to changes in intracortical excitability by measuring short-interval intracortical inhibition, short-interval intracortical facilitation, long-interval intracortical inhibition. Moreover, comparing different modalities with fixed intensity and duration (treadmill vs. cycling) among the same or different populations (e.g., healthy individuals, or healthy vs. stroke) would add further information. Finally, the limited number of studies that looked at the level where the excitability may occur (spinal vs. cortical), and studies on the stroke population have limited the conclusions that could have been drawn if more studies were available for comparison.

CHAPTER 6: CONCLUSION

This scoping review has summarized the available literature about the effect of a single session of acute AE on corticospinal excitability. In healthy individuals, we found that an acute bout of moderate intensity AE with an adequate duration will have a positive effect on corticospinal excitability, while low and high intensity AE did not. There is a trend to suggest that the intensity of the AE is the most important factor. However, if the duration is not sufficient the effect will not be evident. However, there is not enough evidence to support a certain modality of exercise over another (i.e., treadmill vs. cycling). When comparing the spinal level excitability, there was not enough evidence that AE induces the excitability at spinal level in the studies included. Regarding individuals who have experienced a stroke, although studies were limited in number, it was observed that a short duration of high intensity AE can induce corticospinal excitability in the lesioned hemisphere. This finding may be applicable for use in rehabilitation programs in clinical settings. Lastly, more comparative studies are needed to characterize the optimal intensity, duration, and modality as well as other characteristics of AE to best induce an increase in corticospinal excitability.

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APPENDIX 1: PRESS Guideline

PRESS Guideline

Search Submission & Peer Review Assessment

Search Submission

This section to be filled in by the SEARCHER.

Searcher:

Email:

Date submitted:

Date requested by: *Maximum = 5 working days*

Scoping Review Title

This search strategy is…

☐	My PRIMARY (core) database strategy – First time submitting a strategy for search question and database
☐	My PRIMARY (core) strategy – Follow-up review, NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
☐	SECONDARY search strategy – First time submitting a strategy for search question and database
☐	SECONDARY search strategy – NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Databases

Add more rows to the table as needed **Mandatory*

Database(s) (e.g. MEDLINE, CINAHL)	**Interface(s) (e.g. Ovid, EBSCO)**

Research Question +

Describe the purpose of the search

PICOs Format

Outline the PICOs for your question – i.e. Patient, Intervention, Comparison, Outcome, and Study Design – as applicable

Full Review Question *Provide the full review question in sentence format, and then break up the question according to the PICO framework (or other frameworks as appropriate).*	
Population	
Intervention	
Comparison	
Outcome	

PICO	Inclusion Criteria	Exclusion Criteria
Population		
Intervention		
Comparison		
Outcomes		

Was a search filter applied?

Yes ☐ No ☐

If YES, which one(s) (e.g. Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the sources if this is a published filter. **Mandatory if YES*

Other Comments

Other notes or comments you feel would be useful for the peer reviewer **Optional*

/Search Strategy

Please copy and paste your search strategy and translations (optional) here, exactly as run, including the number of hits per line. **Mandatory*

Peer Review Assessment

This section to be filled in by the REVIEWER.

Reviewer:

Email:

Date completed:

1. Translation –

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

If "B" or "C", please provide an explanation or example:

2. Boolean and Proximity Operators

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

If "B" or "C", please provide an explanation or example:

3. Subject Headings

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

If "B" or "C", please provide an explanation or example:

4. Text Word Searching

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

If “B” or “C”, please provide an explanation or example:

5. Spelling, Syntax, and Line Numbers

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

If “B” or “C”, please provide an explanation or example:

6. Limits and Filters

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

If “B” or “C”, please provide an explanation or example:

Overall Evaluation

Note: If one or more “revision(s) required” is noted above, the response below must be “revision(s) required”

A – No revisions	☐
B – Revision(s) suggested	☐
C – Revision(s) required	☐

Additional comments:

APPENDIX 2: Databases Search

Embase search:

No.	Query	Results
#19	11 AND 15 AND 18	164
#18	OR/16-17	207138
#17	((single OR one OR acute) NEAR/3 (session OR event OR bout OR exercise OR training OR dose)):ti,ab,kw	207135
#16	'acute exercise'/exp OR 'acute exercise':ti,ab,kw OR 'acute bout':ti,ab,kw	4738
#15	OR/12-14	15091
#14	'motor evoked potential'/exp OR 'motor evoked potential':ti,ab,kw	14386
#13	'cortico excitability':ti,ab,kw OR 'corticomotor excitability':ti,ab,kw	430
#12	'corticospinal excitability'/exp OR 'corticospinal excitability':ti,ab,kw	1625
#11	OR/1-10	2954140
#10	run*:ab,ti OR walk*:ab,ti OR jog*:ab,ti OR sprint*:ab,ti OR treadmill*:ab,ti OR row*:ab,ti OR swim*:ab,ti OR bicycl*:ab,ti OR cycl*:ab,ti	1943262
#9	(activ* NEAR/2 life*):ab,ti,kw	16053
#8	(physical* NEAR/5 (fit* OR activ* OR movement* OR train* OR condition* OR program*)):ab,ti,kw	220019
#7	((weight* OR strength* OR enduranc* OR circuit* OR interval) NEAR/5 (program* OR train* OR session*)):ab,ti,kw	54814
#6	exercis*:ab,ti,kw OR sport*:ab,ti,kw OR fitness*:ab,ti,kw OR gym*:ab,ti,kw OR aerobic*:ab,ti,kw	636198
#5	'sport'/exp	168215
#4	'training'/de OR 'endurance'/de OR 'exercise tolerance'/de OR 'physical capacity'/de	134472
#3	'physical activity'/exp OR 'physical activity, capacity and performance'/de	419111
#2	'kinesiotherapy'/exp	80893
#1	'exercise'/exp	349151
	Uploaded to Covidence 159 (5 duplicates removed)	

Medline search:

1	Evoked Potentials, Motor/ or Cortical Excitability/	9418
2	("cortico excitability" or "motor evoked potential" or "corticospinal excitability" or "corticomotor excitability").ti,ab,kw,kf.	3851
3	1 or 2	10863
4	exp Exercise/	194184
5	Endurance Training/	199
6	Exercise Tolerance/	12631
7	exp Sports/	182048
8	(training or "physical capacity").ti,ab,kw,kf.	410750
9	(exercis* or sport* or fitness* or gym* or aerobic*).ti,ab,kw,kf.	493947
10	((weight* or strength* or enduranc* or circuit* or interval) adj5 (program* or train* or session*)).ti,ab,kw,kf.	41874
11	(physical* adj5 (fit* or activ* or movement* or train* or condition* or program*)).ti,ab,kw,kf.	163304
12	(activ* adj2 life*).ti,ab,kw,kf.	11267
13	(run* or walk* or jog* or sprint* or treadmill* or row* or swim* or bicycl* or cycl*).ti,ab,kw,kf.	1529380
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	2413046
15	(acute exercise or acute bout).ti,ab,kw,kf.	3893
16	((single or one or acute) adj3 (session or event or bout or exercise or training or dose)).ti,ab,kw,kf.	146433
17	15 or 16	146433
18	3 and 14 and 17	153
	Uploaded to Covidence 55 (98 duplicates removed)	

CINAHL Search:

#	Query	Results
S20	S3 AND S16 AND S19	96
S19	S17 OR S18	54,023
S18	TI ((single or one or acute) N3 (session or event or bout or exercise or training or dose)) OR AB ((single or one or acute) N3 (session or event or bout or exercise or training or dose))	53,576

S17	TI (acute exercise or acute bout) OR AB (acute exercise or acute bout)	3,106
S16	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	650,340
S15	TI (training or "physical capacity") OR AB (training or "physical capacity")	202,842
S14	TI (exercis* or sport* or fitness* or gym* or aerobic*) OR AB (exercis* or sport* or fitness* or gym* or aerobic*)	191,727
S13	TI ((weight* or strength* or enduranc* or circuit* or interval) N5 (program* or train* or session*)) OR AB ((weight* or strength* or enduranc* or circuit* or interval) N5 (program* or train* or session*))	23,873
S12	TI (physical* N5 (fit* or activ* or movement* or train* or condition* or program*)) OR AB (physical* N5 (fit* or activ* or movement* or train* or condition* or program*))	89,438
S11	TI (run* or walk* or jog* or sprint* or treadmill* or row* or swim* or bicycl* or cycl*) OR AB (run* or walk* or jog* or sprint* or treadmill* or row* or swim* or bicycl* or cycl*)	197,973
S10	(MH "Sports+")	87,141
S9	(MH "Exercise Tolerance")	4,872
S8	(MH "Endurance Training")	256
S7	(MH "Aerobic Exercises")	7,392
S6	(MH "Physical Performance")	5,649
S5	(MH "Physical Activity")	46,626
S4	(MH "Exercise+")	120,324
S3	S1 OR S2	2,605
S2	TI (corticospinal excitability OR cortico excitability OR motor evoked potential or corticomotor excitability) OR AB (corticospinal excitability OR cortico excitability OR motor evoked potential OR corticomotor excitability)	1,384
S1	(MH "Evoked Potentials, Motor")	2,060
	Uploaded to Covidence 45 (51 duplicates removed)	

SPORTDiscus Search:

#	**Query**	**Results**
S15	S3 AND S11 AND S14	72
S14	S12 OR S13	24,558

S13	TI ((single or one or acute) N3 (session or event or bout or exercise or training or dose)) OR AB ((single or one or acute) N3 (session or event or bout or exercise or training or dose))	24,048
S12	TI (acute exercise or acute bout) OR AB (acute exercise or acute bout)	4,417
S11	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	853,954
S10	TI kinesiotherapy OR AB kinesiotherapy	120
S9	(((DE "EXERCISE") OR (DE "EXERCISE therapy")) OR (DE "EXERCISE therapy")) OR (DE "PHYSICAL activity")	108,021
S8	TI (training or "physical capacity") OR AB (training or "physical capacity")	158,788
S7	TI (exercis* or sport* or fitness* or gym* or aerobic*) OR AB (exercis* or sport* or fitness* or gym* or aerobic*)	514,537
S6	TI ((weight* or strength* or enduranc* or circuit* OR interval) N5 (program* or train* or session*)) OR AB ((weight* or strength* or enduranc* or circuit* OR interval) N5 (program* or train* or session*))	36,902
S5	TI (physical* N5 (fit* or activ* or movement* or train* or condition* or program*)) OR AB (physical* N5 (fit* or activ* or movement* or train* or condition* or program*))	85,466
S4	TI (run* or walk* or jog* or sprint* or treadmill* or row* or swim* or bicycl* or cycl*) OR AB (run* or walk* or jog* or sprint* or treadmill* or row* or swim* or bicycl* or cycl*)	292,967
S3	S1 OR S2	2,197
S2	TI (corticospinal excitability OR cortico excitability OR motor evoked potential OR corticomotor excitability) OR AB (corticospinal excitability OR cortico excitability OR motor evoked potential OR corticomotor excitability)	540
S1	DE "EVOKED potentials (Electrophysiology)"	1,840
	Uploaded to Covidence 22 (50 duplicates removed)	

APPENDIX 3: PRISMA-ScR Guidelines

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Click here to enter text.
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Click here to enter text.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Click here to enter text.
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Click here to enter text.
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Click here to enter text.
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years	Click here to enter text.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Click here to enter text.
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Click here to enter text.
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Click here to enter text.
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Click here to enter text.
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Click here to enter text.
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Click here to enter text.
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Click here to enter text.
RESULTS			

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Click here to enter text.
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Click here to enter text.
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Click here to enter text.
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Click here to enter text.
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Click here to enter text.
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Click here to enter text.
Limitations	20	Discuss the limitations of the scoping review process.	Click here to enter text.
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Click here to enter text.
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Click here to enter text.

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850

APPENDIX 4: Data Extraction Form

Identification				Population							
Study No.	Author(s)	Year of publication	Origin/country	Sex		Age	Study Individuals		Stroke		
				M	**F**	**Mean**	**Healthy**	**Stroke**	**Lesion side**	**limbs affected**	**time since stroke**

Questionnaires		
TMS screening	**Physical assessment (PAR-Q)**	**Physical Activity Level (IPA-Q)**

Methods										
Assessment			Modality			TMS-Obtained /Muscle Tested				
Corticospinal	**Spinal Excitability**	**CSE and SE**	**Single-pulseTMS Y/N**	**Digi-timer stimulation H-reflex**	**Other**	**Muscle**	**Exercised Muscle**	**Non-Exercised Muscle**	**Upper limb?**	**Lower Limb?**

(continue) Methods					
Intervention					
MAX Test (GXT)	**modality of EX**	**Intensity of EX (Low, Moderate, or High)**	**Duration of EX**	**Warm-up**	**Cool-down**

Outcomes		Comments
Corticospinal excitability changes post AE	Spinal excitability changes post AE	
TMS measure (S-R curve, I/O curve, fixed intensity, Mean MEPs, and Single MEP)	**H-reflex amplitude, H-reflex/M-max recruitment curve, stretch reflex, or late responses**	

APPENDIX 5: CASP Checklist

www.casp-uk.net
info@casp-uk.net
Summertown Pavilion, Middle Way Oxford OX2 7LG

CASP Checklist: 12 questions to help you make sense of a Cohort Study

How to use this appraisal tool: Three broad issues need to be considered when appraising a cohort study:

- Are the results of the study valid? (Section A)
- What are the results? (Section B)
- Will the results help locally? (Section C)

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

About: These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Cohort Study) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

CASP
Critical Appraisal Skills Programme

Paper for appraisal and reference: .....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes ☐
Can't Tell ☐
No ☐

HINT: A question can be 'focused' in terms of
- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments:

2. Was the cohort recruited in an acceptable way?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for selection bias which might compromise the generalisability of the findings
- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments:

Is it worth continuing?

CASP
Critical Appraisal Skills Programme

3. Was the exposure accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for measurement or classification bias
- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

4. Was the outcome accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for measurement or classification bias
- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- has a reliable system been established for detecting all the cases (for measuring disease occurrence)
- were the measurement methods similar in the different groups
- were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

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5. (a) Have the authors identified all important confounding factors?

Yes ☐
Can't Tell ☐
No ☐

HINT:
- list the ones you think might be important, and ones the author missed

Comments:

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes ☐
Can't Tell ☐
No ☐

HINT:
- look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

6. (a) Was the follow up of subjects complete enough?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes ☐
Can't Tell ☐
No ☐

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Comments:

Section B: What are the results?

7. What are the results of this study?

HINT: Consider
- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments:

8. How precise are the results?

HINT:
- look for the range of the confidence intervals, if given

Comments:

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9. Do you believe the results?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- big effect is hard to ignore
- can it be due to bias, chance or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider whether
- a cohort study was the appropriate method to answer this question
- the subjects covered in this study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- you can quantify the local benefits and harms

Comments:

11. Do the results of this study fit with other available evidence?

Yes ☐
Can't Tell ☐
No ☐

Comments:

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12. What are the implications of this study for practice?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- for certain questions, observational studies provide the only evidence
- recommendations from observational studies are always stronger when supported by other evidence

Comments:

APPENDIX 6 A: CASP Checklist Summary

Study No.	Author(s)	Year	CASP Checklist Summary												
			Q1	Q2	Q3	Q4	Q5-A	Q5-B	Q6-A	Q6-B	Q7	Q8	Q9	Q10	Q11	Q12
1	Singh	2014	Y	Y	N	Y	N	N	Y	Y			CT	Y	Y	CT
2	McDonnell	2013	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	CT
3	Mooney	2016	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	CT
4	Garnier	2017	Y	Y	N	Y	Y	N	Y	Y			CT	CT	Y	Y
5	Elsayes	2019	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	Y
6	Smith	2014	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	CT
7	Lulic	2017	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	Y
8	Morris	2020	Y	Y	N	Y	N	N	Y	Y			N	Y	Y	CT
9	Smith	2018	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	CT
10	MacDonald	2019	Y	Y	Y	Y	Y	N	Y	Y			Y	Y	Y	Y
11	Baltar	2018	Y	Y	Y	Y	Y	Y	Y	Y			Y	Y	Y	Y
12	Andrews	2020	Y	Y	Y	Y	Y	N	Y	Y			Y	Y	Y	CT
13	Li	2019	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	Y
14	Boyne	2019	Y	Y	Y	Y	N	N	Y	Y			N	Y	CT	CT
15	Murdoch	2016	Y	Y	Y	Y	Y	N	Y	Y			Y	Y	CT	CT
16	Neva	2017	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	CT
17	Yamazaki	2019	Y	Y	Y	Y	N	N	Y	Y			Y	Y	Y	CT

APPENDIX 6 B: CASP Checklist Summary

Study No.	Author(s)	Year	CASP Checklist Summary	
			Q7	Q8
1	Singh	2014	Moderate intensity cycling exercise did not change the corticospinal excitabilty within the non-exercised muscle	Results lack precision. See Figure 1 for SEM values
2	McDonnell	2013	Neither low nor moderate intensity cycling exercise affected the corticospinal excitability within the non-exercis	Unable to determine - data is not shown
3	Mooney	2016	Moderate intensity cycling exercise did not modulate corticospinal excitabilty within the non-exercised muscle	Unable to determine - data is not shown
4	Garnier	2017	Significant changes in corticospinal excitability within the non-exercised muscle following moderate intensity treadmill (uphill and downhill) exercises (post 30 min)	Results appear precise based on means and SE (see Figure 6)
5	Elsayes	2019	Increase in corticospinal excitability after 20 min of AE similarly between females and males groups	Results appear precise based on means and SD values (see Table 5 and Figure 3)
6	Smith	2014	Low-moderate and moderate to high intensities of cycling exercise did not affect corticospinal excitability within non-exercised muscle	Results appear precise based on mean and SEM values (see Figure 2)
7	Lulic	2017	Increase in corticospinal excitability observed in the non-exercised muscle after 20 min of moderate intensity cycling exercise within the high physical activity level group, but not within the low physical activity level group	Results appear precise based on CI values (see Table 1) and SEM values (see Figure 2)
8	Morris	2020	No changes were observed in corticospinal excitability after a bout of 30 min of low intensity AE separated by executive cognitive tasks	Results lack precision based on SD values (see Table 2)
9	Smith	2018	High intensity cycling exercise did not affect corticospinal excitability within the non-exercised muscle	Results appear precise based on mean and SEM values (see Figure 2)
10	MacDonald	2019	Increase in corticospinal excitability observed in the non-exercised muscle after 20 min of moderate cycling exercise, but not after low intensity cycling exercise	Results lack precision based on means and SD values (see Table 2)
11	Baltar	2018	A decrease in corticospinal excitability was observed after high intensity treadmill exercise, and an increase in corticospinal excitability within the exercised muscle after 15 min of moderate intensity treadmill exercise, but not after low intensity exercise	Results appear precise based on mean and SD values (see Figure 1)
12	Andrews	2020	A single bout of moderate intensity exercise did not enhance corticospinal excitability within non-exercised muscle	Results appear precise based on SD values
13	Li	2019	Corticospinal excitability was increased after a short bout of high intensity treadmill exercise within the lesioned hemisphere (within the non-exercised muscle) post-stroke	Results appear precise based on CI values (see Figure 2)
14	Boyne	2019	No change was detected in corticospinal excitability within the exercised muscle after a session of moderate intensity treadmill exercise	Results lack precision based on CI values
15	Murdoch	2016	Low intensity cycling exercise did not change corticospinal excitability within non-exercised muscle post-stroke	Results appear precise based on mean and SD values (see Figure 4)
16	Neva	2017	No changes were detected in corticospinal excitability or spinal level excitability after a session of moderate intensity cycling exercise within a non- exercised muscle	Results appear precise based (see Table 1 and Figure 5)
17	Yamazaki	2019	No changes in corticospinal excitability or spinal level excitability ws observed after 30 min of low intensity cycling exercise within the exercised or non-exercised muscles	Results appear precise based on mean and SE values (see Table S.2)