Can Anodal tDCS of the Motor Cortex Affect Exercise Performance of the Ipsilateral or Contralateral Knee Extensors?

By

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Abstract

Transcranial direct current stimulation (tDCS) has risen in popularity over the past two decades, in part due to research suggesting it can be used to provide muscular performance improvements; namely increased maximal voluntary force production and reduced fatigue. While substantial conflict in the literature exists as to whether tDCS is truly an effective ergogenic aid, studies almost exclusively examine performance in muscles contralateral to the stimulated cortical area. This leaves a substantial gap in understanding about how muscles ipsilateral to the stimulated site are affected. Additionally, with most participants involved in studies utilizing tDCS being male, and no studies directly comparing the effects between sexes, the viability of tDCS to increase exercise performance for female participants is not well understood.

Keywords: Endurance, Fatigue, Force, Strength

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A version of the literature review from Chapter 2 has been published. Dr. Armin Kibele's contributions to the published review consisted of a critical final review of the manuscript, without any major changes suggested.

Savoury R., Kibele A., Behm D. G. (2021) Methodological Issues with Transcranial Direct Current Stimulation for Enhancing Muscle Strength and Endurance: A Narrative Review. *Journal of Cognitive Enhancement*, https://doi.org/10.1007/s41465-021-00222-7

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List of Abbreviations

a-tDCS – anodal transcranial direct current stimulation

CNS – central nervous system

c-tDCS – cathodal transcranial direct current stimulation

DLPFC – dorsolateral prefrontal cortex

EF – elbow flexors

EMG – electromyography

HRV_{th} – heart rate variability threshold

IC – insular cortex

HD-tDCS – high definition transcranial direct current stimulation

IHI – interhemispheric inhibition

KE – knee extensors

KF- knee flexors

M1 – motor cortex

mA – milliamps

MVC – maximal voluntary contraction

MVIC – maximal voluntary isokinetic contraction

PFC – prefrontal cortex

RMS – root mean squared

s-tDCS – sham transcranial direct current stimulation

tDCS – transcranial direct current stimulation

TC – temporal cortex

TMS – transcranial magnetic stimulation

TTE – time to exhaustion

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Chapter 1: Introduction

Overview

In recent years, there has been a substantial increase in studies utilizing transcranial direct current stimulation (tDCS). This method of non-invasive brain stimulation has been used in many studies interested in understanding its efficacy in both treating a variety of clinical conditions (Alonzo et al., 2013; Fang & Wang, 2021; Brunelin et al., 2012; Pereira et al., 2013; Treister et al., 2015) and usage for performance enhancement, with the latter being of particular interest for this thesis. Many studies up to this point have investigated whether tDCS can provide enhancements to maximal muscle force production and fatigue endurance, with many finding tDCS an effective aid (Tanaka et al., 2009; Krishnan et al., 2014; Frazer et al., 2016; Sales et al., 2016; Lattari et al., 2018; Lattari et al., 2020a; Okano et al., 2015; Hazime et al., 2017; Vargas et al., 2018; Angius et al., 2016; Angius et al., 2018; Vitor-Costa et al., 2015; Cogiamanian et al., 2007; Park et al., 2019; Abdelmoula et al., 2016; Williams et al., 2013; Lattari et al., 2016; Lattari et al., 2020b; Oki et al., 2016), and many others finding no significant difference in comparison to the control (Kan et al., 2013; Montenegro et al., 2015; Cogamanian et al., 2007; Giboin & Gruber 2018; Abdelmoula et al., 2016; Lampropoulou & Nowicky, 2013; Angius et al., 2016; Barwood et al., 2016; Angius et al., 2015; Flood et al., 2017; Kan et al., 2013; Radel et al., 2017; Montenegro et al., 2015; Sasada et a; 2017; Muthalib et al., 2013). With nearly all studies testing the effect of tDCS on performance in muscles contralateral to the site of stimulation, only one has investigated the effect on muscles located ipsilaterally (Vargas et al., 2018).

Additionally, to our knowledge, no studies up to this point have directly compared the effects of tDCS on exercise performance between the sexes. With one study showing that the

effects of cathodal tDCS (c-tDCS) are greater and longer lasting in female participants, in comparison to males, it is possible that a similar trend may be observed when the exercise performance is measured following a-tDCS (Kuo et al., 2006).

Purpose

The purpose of this manuscript style thesis is to determine if maximal force production or fatigue of the knee extensors (KE) either contralateral or ipsilateral to the site of stimulation can be altered by 10 minutes of 2 milliamps of anodal tDCS (a-tDCS) to the left motor cortex. A secondary purpose of this research is to assess any potential sex dependent effects of a-tDCS on either maximal force or fatigue endurance of the KE.

Research Questions

1. Will a-tDCS to the motor cortex affect maximal force production or fatigue resistance in the contralateral or ipsilateral KE?

   It is hypothesized that there will be an increase in maximal force production and fatigue resistance in the contralateral, but not ipsilateral, KE in relation to the site of tDCS.
2. Will a-tDCS affect male and female participants to a similar extent?

   It is difficult to form a hypothesis based on the lack of literature surrounding sex dependent effects of a-tDCS. Therefore, this research question is considered exploratory.

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Chapter 2: Review of Literature
Note: A version of this literature review has been published.

Savoury R., Kibele A., Behm D. G. (2021) Methodological Issues with Transcranial Direct Current Stimulation for Enhancing Muscle Strength and Endurance: A Narrative Review. *Journal of Cognitive Enhancement*, https://doi.org/10.1007/s41465-021-00222-7

Abstract

In recent years, there has been a substantial increase in the number of studies investigating the effects that transcranial direct current stimulation (tDCS) can have on exercise performance. Currently, there exists substantial conflict in the literature, with many studies reporting that 10–20 min of tDCS can result in augmented performance, while other studies also report no significant changes. Throughout the literature, there is considerable variance in the tDCS protocols being administered. These differences include electrode placement, stimulation intensity, stimulation duration, and participant's sex. This variance may account for some of the discrepancies in the results of published studies. Therefore, the goal of this review was to explore the differences in tDCS protocols among these studies to help determine which variations seem to be most effective at producing muscle strength and endurance performance increases. It is suggested that a standardized set of protocols would be beneficial in order to make the comparison of the literature more straightforward. Although, as it currently stands, more research in certain areas surrounding various tDCS variables is needed to determine the most optimal setup for increasing exercise performance.

Keywords: tDCS, Fatigue, Force, Performance, NIBS

Introduction to Muscle Fatigue

Muscle fatigue is a reversible phenomenon that can be defined as the transient decrease in the ability of the muscle to produce force as a result of exercise (Gandevia, 2001; Allen et al., 2008). The main groups of factors that have been identified to contribute to fatigue are peripheral and central factors (Behm, 2004; Behm & St. Pierre, 1997; Gandevia, 2001). However, this method of grouping has been called into question by Enoka & Duchateau (2016) who highlighted the various limitations of this approach. Instead, they proposed fatigue be thought of as a disabling symptom where both physical and cognitive functionality are impaired by the interactions between performance fatiguability and perceived fatiguability (Enoka & Duchateau, 2016). However, Steele (2020) suggested that the use of performance and perceived fatiguability adds confusion since the use of the suffix "ability" implies "susceptibility to the original noun". Instead, they suggest that fatigue should refer to the reduction of an individual's capacity to produce force in terms of magnitude or rate. (Steele, 2020).

First, peripheral fatigue results from various factors that occur at points at or distal to the neuromuscular junction (Gandevia, 2001). Since force production in a muscle is generated by the cycling of actin and myosin, much research has been focused on the effects of the accumulation of intracellular metabolites, which are produced as a result of exercise (Dawson et al., 1978; Cooke et al., 1988). Increased metabolite concentration and muscle acidosis has been shown to disrupt muscle function through contractile kinetics, propagation of action potentials and function of enzymes (Cady et al., 1989; Kowalchuk et al., 1984; Kent-Braun, 1999). It has been shown that increased interstitial potassium concentration can decrease force production and excitability of the muscle which can contribute to fatigue (Sejersted & Sjogaard, 2000; Juel, 1986; Nordsborg et al., 2003). While some studies have shown that accumulation of hydrogen

ions can fatigue the muscle through a reduction in force per cross bridge (Fitts, 2008; Knuth et al., 2006), and decreased sensitivity to myofibrillar calcium (Fitts, 2008; Allen et al., 1989), these findings have been disputed (Lamb & Stephenson, 2006; Allen et al., 2008). More recent technological advancements have allowed newer studies to investigate how these metabolites, including hydrogen ions, inorganic phosphate, and adenosine diphosphate affect the contractile proteins of the muscle (Debold, 2012).

Second, there exists central fatigue, which originates in the central nervous system (CNS) and results in a decreased neural drive to the muscle involved in voluntary contraction (Gandevia, 2001). Central fatigue can further be divided into spinal and supraspinal factors (Gandevia, 2001). Spinal factors of fatigue result from an overall reduction in spinal reflex facilitation and an increase in inhibition. This is caused by feedback mechanisms from the altered input from muscle spindles, Golgi tendon organs and group III and IV muscle afferents that innervate the muscle being fatigued (Gandevia, 2001). Supraspinal fatigue refers to the decreased cortical excitability of the motor cortex, which results in decreased stimulation of descending motor tracts and a lower force output (Gandevia, 2001). The effects of supraspinal fatigue have been demonstrated using transcranial magnetic stimulation (TMS), which can modulate the excitability of the motor cortex (Day et al., 1989). While peripheral and central fatigue were once thought to be separate, recent research has indicated that working muscles can modulate the CNS motor output while becoming fatigued (Blain, 2017). Similarly, transcranial direct current stimulation (tDCS) has been used to modulate cortical excitability and has been used in studies investigating fatigue.

Transcranial Direct Current Stimulation

Over the past two decades, there has been a surge in studies involving tDCS. tDCS is a non-invasive brain stimulation technique, that can modulate cortical excitability producing both excitatory and inhibitory effects (Nitsche & Paulus, 2000). tDCS works by creating a circuit by placing two electrodes on the participant's skull and allowing a weak electrical current to pass through. In a unihemispheric setup, one electrode is called the target electrode, which is placed over the area of interest, while the other, reference electrode is placed either in another location on the scalp or in an extracephalic location, such as the shoulder. There are three main stimulation types in tDCS research. First anodal tDCS (a-tDCS) involves placing the anode at the area of interest, then placing the cathode at the reference position allowing a positive current to pass through the target neurones. a-tDCS is thought to depolarize stimulated neurones, increasing their resting potential, thus increasing the likelihood of an action potential occurring (Nitsche et al., 2008). Cathodal tDCS (c-tDCS) involves placing the cathode at the area of interest and the anode at the reference position. This allows a negative current to pass through the targeted neurones which is thought to have the opposite effects described for a-tDCS. The neurones become hyperpolarized which decreases the likelihood of action potentials occurring (Nitsche et al., 2008). Although realistically, the differences between a-tDCS and c-tDCS are not as clear-cut, this general assumption will be made for this review (Monte-Silva et al., 2013; Batsikadze et al., 2013). The final type of stimulation is sham tDCS (s-tDCS), where stimulation is administered for either a very short duration, or a very low current is applied. s-tDCS acts as a control condition.

The effects of tDCS are of interest to many different fields. For example, clinical applications involving treating depression, anxiety, schizophrenia, Parkinson's disease, and

chronic pain have been investigated (Alonzo et al., 2013; Fang & Wang, 2021; Brunelin et al., 2012; Pereira et al., 2013; Treister et al., 2015). However, this review will focus on the effect that tDCS has on maximal muscle force production and fatigue. With studies demonstrating increases in performance following the administration of tDCS, the interest among athletes has grown substantially over the past number of years.

There is significant conflict in the literature on the effects that tDCS has on the ability for muscles to produce force and modulate fatigue resistance. Many studies have reported increased maximal force production following a-tDCS (Tanaka et al., 2009; Krishnan et al., 2014; Frazer et al., 2016; Sales et al., 2016; Lattari et al., 2018; Lattari et al., 2020a; Okano et al., 2015; Hazime et al., 2017; Vargas et al., 2018), while others have found no changes when compared to the control (Kan et al., 2013; Montenegro et al., 2015; Cogamanian et al., 2007; Giboin & Gruber 2018; Abdelmoula et al., 2016; Lampropoulou & Nowicky, 2013). Similarly, various studies have demonstrated an increased fatigue resistance (Angius et al., 2016; Angius et al., 2018; Vitor-Costa et al., 2015; Cogiamanian et al., 2007; Park et al., 2019; Abdelmoula et al., 2016; Williams et al., 2013; Lattari et al., 2016; Lattari et al., 2020b; Oki et al., 2016) while many have also found that a-tDCS had no effect on muscle fatiguability (Angius et al., 2016; Barwood et al., 2016; Angius et al., 2015; Flood et al., 2017; Kan et al., 2013; Radel et al., 2017; Montenegro et al., 2015; Sasada et a; 2017; Muthalib et al., 2013). One study also found that a-tDCS increased fatiguability of the knee extensors (KE) (Giboin & Gruber, 2018). While more studies have reported increased performance measures following a-tDCS, it is important to note that studies where significant differences are found are more likely to be published (Møller & Jennions, 2001). The reported effects of c-tDCS on these outcome measures are more homogenous, with most studies reporting no significant effects on force production or fatigue (Tanaka et al. 2009;

Angius et al., 2018; Vitor-Costa et al., 2015; Cogiamanian et al., 2007; Lattari et al., 2020a; Sasada et al., 2017) and two studies finding an increased susceptibility to fatigue (Lattari et al., 2016; Giboin & Gruber, 2018). Although, it should be noted that while a-tDCS was used in every study included in this review, c-tDCS was only utilized in 31% of studies.

Potential Factors Affecting tDCS and Exercise Performance

There are a plethora of variables that can have an effect on the administration and effectiveness of tDCS. It has been estimated that when accounting for electrode location, size, number, current density, polarity, and stimulation duration, there are between four million to eight trillion individual protocols that can be implemented (Machado et al., 2019a).

Target Electrode Location

Motor Cortex

Throughout the literature reviewed, most studies investigating force production and fatigue placed their target electrodes over the primary motor cortex (M1) (Machado et al., 2019a; Machado et al., 2019b). The stimulation of the M1 is of interest to researchers looking to increase fatigue resistance since it is assumed to control the motor drive which is required to activate motor units (Radel et al., 2017). As previously mentioned, spinal and supraspinal factors of fatigue can result in decrements in the ability of muscles to produce force. This can be attributed to a reduction in the excitability of the motoneurone pool, and a reduction in neural drive from the M1 and other cortical areas making it difficult to compensate for a decrease in spinal excitability (Gandevia, 2001; Taylor et al., 2016; Taylor & Gandevia, 2008). Therefore, a-tDCS induced increases in the excitability of the M1 could result in a sustained neural drive of the motoneurones. This sustained neural drive could result in a delayed decrease of neural drive to exercised muscles thereby delaying the onset of fatigue and increasing performance. Similarly,

an a-tDCS induced increased neural drive could result in an increased motor unit recruitment, thus increasing the ability of muscles to produce maximal force. Another reason the M1 may be of interest to those looking to improve exercise performance with tDCS is modulation of pain perception. While the precise mechanism is unclear, the rationale involves the M1's connections to the insula and thalamus. This connection has been shown in non-human animal models by injecting fluorescent tracers and wheatgerm agglutinin/horseradish peroxidase conjugate into regions of the M1 (Stepniewska et al., 1994). Additionally, many studies have shown that a-tDCS of the M1 can increase sensory and pain threshold in both healthy participants and those with chronic pain (Vaseghi et al., 2014). It has been suggested that athletes who are more adept at tolerating pain can exhibit greater exercise performance, since exercise-induced pain is often considered a major inhibiting factor during exercise (Mauger, 2013). Therefore, stimulation of the M1 could also improve performance through the reduction of exercise induced pain.

The M1 position was determined in one of three ways. The first being the use of TMS, to locate the "hotspot" for the muscle being tested (Giboin & Gruber, 2018; Abdelmoula et al., 2016; Williams et al., 2013; Tanaka et al., 2009; Frazer et al., 2016; Lampropoulou & Nowicky, 2013; Oki et al., 2016; Sasada et al., 2017; Krishnan et al., 2014). Others placed the target electrode at the C3 and C4 locations according to the 10-20 electrode placement system (Hazime et al., 2017; Angius et al., 2015; Montenegro et al., 2015; Flood et al., 2017; Vargas et al., 2018). Three studies found the M1 by measuring four centimeters lateral to the vertex (Cogiamanian et al., 2007; Kan et al., 2013; Muthalib et al., 2013). One study placed the target electrode at the C2 location, according to the 10-20 electrode placement system (Radel et al., 2017). One study did not report their method of locating the M1 (Angius et al., 2016). Five studies found increased maximal force production following a-tDCS of M1 (Tanaka et al., 2009; Frazer et al., 2016,

Hazime et al., 2017; Krishnan et al., 2014; Vargas et al., 2018), four found increased fatigue resistance (Williams et al., 2013; Oki et al., 2016; Cogiamanian et al., 2007; Abdelmoula et al., 2016), eight found no significant changes in maximal force production when compared to the control (Montenegro et al., 2015; Kan et al., 2013; Lampropoulou & Nowicky, 2013; Cogiamanian et al., 2007; Giboin & Gruber, 2018; Abdelmoula et al., 2016; Sasada et al., 2017), six found no significant changes in fatiguability (Angius et al., 2015; Flood et al., 2017; Montenegro et al., 2015; Radel et al., 2017; Muthalib et al., 2013; Kan et al., 2013), one showed improvements along with no change in fatiguability, depending on the location of the reference electrode (Angius et al., 2016), and one reported decreased fatigue resistance (Giboin & Gruber, 2018).

Based on the outcomes of these studies, it seems that the effects of a-tDCS on exercise performance are more common when TMS is used to locate the ideal location for stimulation in comparison to the use of other methods. This makes logical sense since using TMS allows the researcher to locate the hotspot for the muscle group of interest. In contrast, the 10-20 system only corresponds to a general area of the M1 and measuring four centimetres to the right of the vertex of the head might not be accurate for all participants, depending on the dimensions of their heads. This suggests that future studies should use TMS to choose target electrode placement when M1 is the area of interest. Furthermore, 37% of studies investigating force production (5/14) or fatigue endurance (5/13) saw improvements following a-tDCS. This suggests that a-tDCS of the M1 can modulate maximal muscle force production and muscle fatigue resistance to a similar extent.

Some studies have also attempted to modulate both the left and right M1 simultaneously by placing the target electrode between them at the Cz location as described in the 10-20

electrode placement system (Vitor-Costa et al., 2015; Park et al., 2019; Lattari et al., 2020a; Sasada et al., 2017). Stimulating both motor cortices is of particular importance when investigating exercise tasks that require both sides of the body, such as running or jumping. All three of these studies demonstrated performance improvements following a-tDCS. Both studies measuring fatigue reported increased time to exhaustion (TTE), demonstrating that this protocol can be effective in increasing fatigue resistance (Vitor-Costa et al., 2015; Park et al., 2019). Lattari et al. (2020a) demonstrated that a-tDCS can increase jump height, flight time, and peak power in comparison to the baseline suggest that this can also be an effective method to increase muscle force production. Although conversely, two studies reported no change in cycling peak power following anodal stimulation (Sasada et al., 2017; Vitor-Costa et al., 2015). Three of these studies also used a c-tDCS protocol, but none found significant post-test changes (Vitor-Costa et al., 2015; Lattari et al., 2020a; Sasada et al., 2017). In another study by Angius et al. (2018), bilateral a-tDCS to the M1 was administered and demonstrated a 23% increase in cycling TTE, while c-tDCS showed no effects. Angius et al. (2018) also measured maximal voluntary contraction force of the KEs, before and after stimulation, although no significant differences were found for anodal or cathodal tDCS. The results of these studies suggest that anodal stimulation of both motor cortices by either placing the single target electrode on the Cz location or by bilaterally stimulating both M1 areas, can be effective in improving fatigue resistance and muscle force production. More research should be performed to determine if one protocol induces greater effects than the other.

Temporal Cortex

The temporal cortex (TC) has also been the location of the target electrode in multiple studies. The TC is of interest because stimulating this area is thought to increase the excitability

of the insular cortex (IC), which is involved in cardiac autonomic control. Non-human animal studies have suggested that the right IC is responsible for sympathetic modulation, while the left IC is responsible for parasympathetic modulation (Oppenheimer et al., 1990; Oppenheimer et al., 1992; Napadow et al., 2008). When progressing from rest to intense exercise, the parasympathetic system becomes less responsible for cardiac autonomic control until complete vagal withdrawal. This point of withdrawal can be measured using the heart rate variability threshold (HRV_{th}). HRV_{th} has been shown to coincide with ventilatory threshold, which is an important indicator of the shift of exercise intensity domain (Cottin et al., 2006; Cottin et al., 2007). Therefore, delaying HRV_{th} would increase the duration of exercise at a lower cardiovascular load, which may result in the postponement of fatigue.

All studies reviewed used the 10-20 system to locate the TC. Two studies have investigated maximal force production after a-tDCS of the TC (Sales et al., 2016; Okano et al., 2015), while only one study has investigated muscle fatiguability (Barwood et al., 2016). Okano et al. (2015) found a small increase in cycling peak power output (4%) along with an increased TTE. Sales et al. (2016) found increases in total work and peak torque when using maximal voluntary isokinetic contractions (MVIC), both following a-tDCS. Barwood et al. (2016) failed to find any changes in muscle fatiguability when compared to the control.

While only three studies have investigated changes in performance following a-tDCS of the TC, initial findings suggest that stimulation of this area may be more effective for producing increases in maximal force production than modulating muscle fatigue resistance. Although, Okano et al. (2015) also reported increased cardiac efficiency as a result of delayed vagal withdrawal following a-tDCS at submaximal intensities, suggesting that stimulation of the TC may be effective in improving performance at prolonged submaximal intensities. With

conflicting results, and only three studies looking at performance improvements following a-tDCS of the TC, more research should be completed to help further determine the effectiveness of stimulating this region of the brain for exercise performance.

Prefrontal Cortex

The prefrontal cortex (PFC) is another area that has been targeted due to the role it plays in the cognitive control of behaviour. Four studies investigating exercise performance have targeted the PFC. Three of these studies effectively increased fatigue resistance following a-tDCS (Lattari et al., 2016; Lattari et al., 2018; Lattari et al., 2020). An increase in peak cycling power was also reported by Lattari et al. (2018). One other study failed to find any changes in fatiguability following anodal stimulation (Radel et al., 2017). The reason for the conflicting results may be due to the tDCS protocols utilized by each study. For each study by Lattari et al. (2016; 2018; 2020), the target electrode was positioned at the F3 location with the reference electrode at the Fp2 location, as outlined by the international 10-20 electrode placement system. In contrast, the target electrode in the study by Radel et al. (2017) was placed at the AF4 location and utilized high definition tDCS rather than traditional tDCS technology. The high definition tDCS protocol involved placing four reference electrodes surrounding the target electrode, with each reference electrode located 40 millimeters away from the target electrode. High definition tDCS is thought to target the region of interest more focally, thereby minimizing current diffusion into nearby cortical regions (Radel et al., 2017). Therefore, it may be possible that the lack of significant effects found in the study by Radel et al. (2017) are a result of the AF4 not being an effective target location for tDCS stimulation, when the goal is to increase exercise performance. However, it may also be possible that the effects seen in the studies by Lattari et al.

(2016; 2018; 2020) are a result of the tDCS current bleeding into and stimulating surrounding areas of the cortex.

It has been proposed that the PFC has a role in the integration of both the internal and external factors present in exercise environments (Robertson & Marino, 2016). These factors include, but are not limited to, motivation, task endpoint, perceived exertion, physiological sensations, and reward. The PFC is thought to exert a top-down effect, providing a relevant response depending on the situation. This can allow for motor unit derecruitment, or in certain situations, the overriding of these signals thereby prolonging motor output despite downregulation of motor control (Robertson & Marino, 2016). A review suggested that a decreased ability of the PFC to overcome mental fatigue during exercise may reduce exercise performance (Van Cutsem et al., 2017). Additionally, it has been demonstrated that PFC oxygenation is reduced before fatigue occurs (Rupp & Perrey, 2008; Rooks et al., 2010).

High Definition tDCS

It is important to note that due to the nature of tDCS, the targeted area is not the only area that receives stimulation. It is common for current to "bleed" into surrounding areas of the brain (Thair et al., 2017). Therefore, one cannot be certain that changes in the dependent variable are due to alterations in the targeted cortical area, as surrounding areas of the brain may also be affected. For this reason, high definition tDCS (HD-tDCS) has been developed, which uses an electrode array to localize the stimulation to a greater degree than traditional tDCS. Two studies used HD-tDCS and investigated the effects of anodal stimulation on fatigue resistance (Radel et al., 2017; Flood et al., 2017), while one also investigated maximal force production (Flood et al., 2017). One study stimulated the M1 (Flood et al., 2017), while the other stimulated the PFC and M1 (Radel et al., 2017). Both studies used the 10-20 electrode placement system to locate

stimulation areas. Neither of these studies found that anodal stimulation using HD-tDCS was effective at improving muscle endurance or maximal force production. While more research should be done to either support or dispute these findings, this research suggests that areas other than the M1 and PFC may be responsible for changes in endurance found in stimulation of these areas in studies using a traditional tDCS protocol.

Location of Reference Electrode

It is possible that the location of the reference electrode can influence the ability for tDCS to modulate the excitability of the target brain area. Of the studies reviewed, when the M1 area was targeted, the reference electrode was placed on either the contralateral dorsolateral prefrontal cortex (DLPFC) (Angius et al., 2016; Angius et al., 2015), supraorbital area (Montenegro et al., 2015; Tanaka et al., 2009; Williams et al., 2013; Frazer et al., 2016; Giboin & Gruber, 2018; Sasada et al., 2017; Oki et al., 2016; Vargas et al., 2018; Krishnan et al., 2014; Haime et al., 2017), the ipsilateral shoulder/upper arm (Angius et al., 2016; Angius et al., 2018; Kan et al., 2013; Cogiamanian et al., 2007; Lampropoulou & Nowicky, 2013; Muthalib et al., 2013), or contralateral shoulder (Abdelmoula et al., 2016). None of these studies were successful at increasing exercise performance when the reference electrode was placed at the DLPFC. When the reference electrode was placed on the supraorbital area, 71% (5/7) of studies investigating maximal force production reported increases (Tanaka et al., 2009; Frazer et al., 2016; Vargas et al., 2018; Krishnan et al., 2014; Hazime et al., 2017), 50% (2/4) found improvements in fatigue resistance (Williams et al., 2013; Oki et al., 2016), and 25% (1/4) found decreased fatigue resistance following a-tDCS (Giboin & Gruber, 2018). When the reference electrode was located at the shoulder, no studies reported an increase in maximal force production, however 67% (4/6) of studies found an increased fatigue resistance (Angius et al., 2016; Angius et al., 2018;

Cogiamanian et al., 2007; Abdelmoula et al., 2016). Thus far, only one study has investigated the effects of varying reference electrode placement on exercise performance (Angius et al., 2016). This study compared placing the reference electrode at the DLPFC and shoulder area. They found that when placed at the DLPFC, no changes in TTE were found, however there was an increase in TTE when the reference electrode was placed at the shoulder.

The findings from these studies suggest that placing the reference electrode at either the supraorbital area or shoulder area is more effective for inducing exercise performance enhancements in comparison to the DLPFC. However, since only two studies have placed the reference electrode at the DLPFC, more research should be done to strengthen this hypothesis. In addition, it appears that placing the reference electrode on the supraorbital area can be effective at increasing maximal muscle force production and increasing fatigue resistance. In comparison, placing the reference electrode at the shoulder seems effective at increasing fatigue resistance, but not effective at increasing maximal force production. Although, with relatively few studies completed, research comparing the effects between placing the reference electrode on the supraorbital area and the shoulder area would be of interest. A potential rationale for placing the reference cathode in an extracephalic location rather than a cephalic is to avoid unwanted cathodal stimulation of other cortical areas. Since cathodal stimulation is thought to reduce cortical excitability (Nitsche et al., 2008), placing the cathode where it cannot modulate any cortical area may be beneficial. Although, with some studies finding increased maximal force production with the reference cathode stimulating the supraorbital area, there may be a mechanism where cathodal stimulation of this area allows for increased motor unit recruitment and/or firing frequency.

Stimulation Intensity

All studies reviewed used a stimulation protocol with a stimulation intensity ranging from 1.5-2.0 milliamps (mA) with a duration from 10-20 minutes. This is in accord with standard safety precautions for tDCS that suggest using an intensity below 2 mA (Iyer et al., 2005). While it would seem logical that an increased stimulation intensity would result in a longer duration of effects and/or greater effects, this does not seem to be the case. Some studies have shown that increasing current intensity does not result in longer neuroplastic effects (Batsikadze et al., 2013; Monte-Silva et al., 2013). Furthermore, a study that investigated the effects of four different current intensities (0.5, 1, 1.5, 2 mA) applied over a 15-minute duration found no significant differences in cortical excitability induced by the various intensities following a-tDCS (Jamil et al., 2017). Of the studies reviewed that target the M1, five used a stimulation intensity of 1.5 mA (Cogiamanian et al., 2007; Abdelmoula et al., 2016; Williams et al., 2013; Lampropoulou & Nowicky, 2013; Oki et al., 2016), and 14 used an intensity of 2 mA (Angius et al., 2016; Angius et al., 2018; Angius et al., 2015; Tanaka et al., 2009; Giboin & Gruber, 2018; Kan et al., 2013; Flood et al., 2017; Hazime et al., 2017; Frazer et al., 2016; Montenegro et al., 2015; Sasada et al., 2017; Muthalib et al., 2013; Radel et al., 2017; Vargas et al., 2018; Krishnan et al., 2014). Four studies using 1.5 mA of current saw increases in fatigue resistance following anodal stimulation (Cogiamanian et al., 2007; Abdelmoula et al., 2016; Williams et al., 2013; Oki et al., 2016), while the other study using this protocol did not test fatigue (Lampropoulou & Nowicky 2013). Three of these studies also tested maximal force production, with none of them finding changes in comparison to the control (Cogiamanian et al., 2007; Abdelmoula et al., 2016; Lampropoulou & Nowicky 2013). In studies using 2 mA of current, 42% (5/12) found improvements in maximal force production (Tanaka et al., 2009; Hazime et al., 2017; Frazer et al., 2016; Vargas

et al., 2018; Krishnan et al., 2014), with the others finding no significant changes (Kan et al., 2013; Flood et al., 2017; Angius et al., 2016; Angius et al., 2018; Giboin & Gruber, 2018; Montenegro et al., 2015). In addition, 20% (2/10) of studies using 2mA found increased muscle fatigue resistance (Angius et al., 2016; Angius et al., 2018), 10% (1/10) found decreased fatigue resistance (Giboin & Gruber, 2018), and 70% (7/10) found no change (Angius et al., 2016; Angius et al., 2015; Kan et al., 2013; Flood et al., 2017; Montenegro et al., 2015; Muthalib et al., 2013; Radel et al., 2017).

These findings suggest that 1.5 mA of current intensity may be more effective at increasing fatigue resistance in comparison to 2 mA of current, however, the opposite may be true with regards to maximal force production. Future studies directly comparing differences in performance changes at various current intensities would provide valuable insight. The effects of current intensity may also vary based on stimulation duration, location, and polarity and should be investigated further.

Stimulation Duration

Like modulation of stimulation intensity, increases in stimulation duration do not necessarily lead to greater or prolonged effects on the participant. A study by Monte-Silva et al. (2013), showed that a 26-minute a-tDCS protocol resulted in inhibitory changes rather than excitatory. In addition, 20 minutes of c-tDCS has been shown to result in excitatory changes rather than inhibitory (Batsikadze et al., 2013). Of the reviewed studies targeting M1 with a current intensity of 2 mA, durations of 10 (Angius et al., 2016; Angius et al., 2018; Angius et al., 2015; Tanaka et al., 2009; Giboin & Gruber, 2018; Kan et al., 2013; Muthalib et al., 2013), 15 (Sasada et al., 2017) and 20 (Flood et al., 2017; Hazime et al., 2017; Frazer et al., 2016; Montenegro et al., 2015; Vargas et al., 2018) minutes were used. In one study, the stimulation

duration ranged from 10-20 minutes depending on when the participant TTE test ended (Radel et al., 2017). Of the studies that used a 10-minute stimulation period for a-tDCS, two found increases in maximal force production (Tanaka et al., 2009; Krishnan et al., 2014), two found increased fatigue resistance (Angius et al., 2016; Angius et al., 2018), one found a decrease in fatigue resistance (Giboin & Gruber, 2018), four found no change in maximal force production (Giboin & Gruber, 2018; Kan et al., 2013; Angius et al., 2016; Angius et al., 2018), and four found no change in muscle fatiguability (Kan et al., 2013; Muthalib et al., 2013; Angius et al., 2015; Angius et al., 2016). When a 20-minute protocol was used, no studies saw an increase in fatigue resistance (Flood et a., 2017; Montenegro et al., 2015; Vargas et al., 2018), but two studies saw improvements in maximal force production (Hazime et al., 2017; Vargas et al., 2018) with one other showing no changes (Montenegro et al., 2015). The study by Sasada et al. (2017) that used a 15-minute protocol, saw no changes in maximal force production, while the study by Radel et al. (2017) which used variable stimulation durations, saw no changes in fatigue resistance.

While these findings suggest that 10-minute protocols are more effective at increasing fatigue resistance in muscles than 20-minute protocols, the reverse seems to be true for inducing increases in a muscle's ability to produce maximal force. It would be of interest to see a study compare differing stimulation durations on a muscle group's ability to produce force and combat fatigue.

Performance Measurement

Throughout the literature, when the M1 is targeted, there have been a variety of muscle groups and exercises investigated. When investigating fatigue resistance, submaximal TTE tests were commonly used. Of three a-tDCS studies that used a cycling TTE test, two reported

increases (Angius et al., 2018; Vitor-Costa et al., 2015), while the other studies reported no improvements (Angius et al., 2015). With seven a-tDCS studies that used elbow flexor TTE tests to investigate fatigue resistance, four reported increased TTE (Cogiamanian et al., 2007; Abdelmoula et al., 2016; Williams et al., 2013; Oki et al., 2016), while the others reported no changes (Muthalib et al., 2013; Kan et al., 2013: Radel et al., 2017). Two studies used a KE TTE test (Angius et al., 2016; Flood et al., 2017) The study by Angius et al. (2016) found both increased TTE and no change for the extracephalic and cephalic electrode placement protocols, respectively, while Flood et al. (2017) did not report any changes in comparison to the control. Another study used a running TTE test (Park et al., 2018) and found improvements following a-tDCS. One study used a fatigue index test to examine fatigue following tDCS (Montenegro et al., 2015). This involved participants performing three sets of 10 MVICs of the knee flexors and extensors. Fatigue was monitored as the percent difference between the first and last third of repetitions in each set. a-tDCS did not result in any significant changes in fatigability in comparison to the sham protocol.

Thus far, there has been research investigating the effects of tDCS on fatiguability on various muscle groups throughout the body when the M1 is targeted. Of these studies, 50% (8/16) have shown increased fatigue resistance following a-tDCS. Of the muscle groups investigated, the elbow flexors seem particularly susceptible to these effects, with 57% (4/7) of studies showing increases in TTE following tDCS (Cogiamanian et al., 2007; Abdelmoula et al., 2016; Williams et al., 2013; Oki et al., 2016). Four studies have investigated the effects of tDCS on KE fatiguability, with one showing mixed results (Angius et al., 2016), one showing increased susceptibility to fatigue (Giboin & Gruber, 2018) and the others showing no changes (Montenegro et al., 2015; Radel et al., 2017; Muthalib et al. 2013). More studies investigating

these muscle groups should be completed to support or refute these findings. Sixty seven percent (67%, 2/3) of studies investigating cycling TTE found improvements, however, two of these three studies stimulated both motor cortices (Angius et al., 2018; Vitor-Costa et al., 2015). The study which failed to find changes stimulated their target area unihemispherically (Angius et al., 2015). Since cycling utilizes both the left and right sides of the body, it would make sense that stimulating only one hemisphere would not be as effective as stimulating bihemispherically. Further studies, utilizing bihemispheric protocols should be completed for bilateral movements to expand on the results of these studies.

Studies investigating changes in force production following tDCS of the M1, have all used MVCs for measurement. Studies have investigated elbow flexors (Lampropoulou & Nowicky, 2013; Kan et al., 2013; Krishnan et al., 2014), wrist flexors (Frazer et al., 2016), rotator cuff muscles (Hazime et al., 2017), KE (Giboin & Gruber, 2018; Montenegro et al., 2015; Vargas et al., 2018: Angius et al., 2016), knee flexors (Montenegro et al., 2015) and toe pinch force (Tanaka et al., 2009). Of these studies, 45% (5/11) showed improvements to MVC force/torque following tDCS (Frazer et al., 2016; Hazime et al., 2017; Tanaka et al., 2009; Krishnan et al., 2014; Vargas et al., 2018). While it does appear that tDCS can cause increases in maximal force production, there are very few studies investigating each muscle group. Therefore, more studies should be done to determine whether some muscle groups are more susceptible to these effects than others.

Ipsilateral Versus Contralateral Muscles

When unihemispheric stimulation was employed, only one study tested muscles ipsilateral to the site of stimulation (Vargas et al., 2018). This study found no significant changes in maximal force production of the KE following a-tDCS of the ipsilateral motor cortex,

although significant changes in the contralateral KE were present. This result would be expected, since most axons of the corticospinal tract cross to the contralateral side of the body and thus each brain hemisphere primarily controls the contralateral side of the body (Welniarz et al., 2017). Although, there is evidence of cross talk between hemispheres as found in studies investigating cross-education (Carroll et al., 2006), and non-local or crossover muscle fatigue (Behm et al. 2021). In addition, no studies have tested the effect of tDCS on fatigue in muscles ipsilateral to the site of stimulation. Since interhemispheric connections via the corpus callosum (Carson, 2005; Carroll et al., 2006) as well as ipsilateral tracts such as the reticulospinal and rubrospinal tracts could influence ipsilateral activation (Brown, 1981), greater exploration of this issue should be conducted.

Participants' Sex

Of the studies reviewed, females made up just 29% (110/377) of participants. Furthermore, female participants were used in only 50% (14/28) of studies with no studies comparing the effects of tDCS on maximal force production or muscle fatiguability between the sexes. This lack of comparison leaves a significant gap in knowledge. Future studies should recruit both male and female participants, while also directly comparing the results of the two in order to help determine if tDCS affects these performance outcomes differently depending on the participants' sex. While no studies have compared the effects of tDCS on exercise performance between the sexes, one study has shown sex differences in tDCS induced neuroplasticity of the M1 (Kuo et al., 2006). It was found that the effects of c-tDCS were greater and lasted longer in female participants when compared to males. This was hypothesized to be related to the difference in sex hormones, and their effects on neuroplasticity. (Kuo et al., 2006)

Conclusion

There are many variables involved in the administration of tDCS. This makes it difficult to directly compare studies as any one variable could impact the effects of tDCS on cortical excitability, and thus performance. Overall, it seems that a-tDCS can increase maximal muscle force production and fatigue endurance to some extent, although the varying of protocols seem to have a substantial effect. Therefore, it would be beneficial to develop a set protocol for studies investigating the effects of tDCS on performance, to help make comparison of the literature more straightforward. Creating a standardized set of protocols with the current body of literature would be difficult since some protocol variations have received little attention thus far. Therefore, more research into these variables would be necessary to determine the most effective tDCS protocol for inducing performance enhancements. This includes more research targeting areas other than the M1, such as the TC, and PFC. Studies which vary the stimulation intensity and duration of tDCS while measuring exercise performance would also be beneficial.

While fatigue of muscles contralateral to the site of tDCS has been commonly studied, only one study has investigated the effects on muscle ipsilateral to the site of stimulation (Vargas et al., 2018). Recently, there has been a significant amount of research into the effects that fatiguing a muscle has on other muscles throughout the body. Communication between the hemispheres has been thought of as a potential mechanism for these crossover effects. Therefore, more testing of muscles ipsilateral to the site of stimulation may provide evidence of this pathway.

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Chapter 3: Reduced Isometric Knee Extensor Force Following Anodal Transcranial Direct Current Stimulation of the Ipsilateral Motor Cortex

Abstract

The main goal of this study is to determine if 10 minutes of anodal transcranial direct current stimulation (a-tDCS) to the left motor cortex is capable of modulating either maximal voluntary force production or fatigue endurance of the quadriceps either contralateral or ipsilateral to the site of stimulation. A secondary goal of this research was to investigate the possibility of sex-dependent effects of a-tDCS on maximal voluntary force production and fatigue endurance. In a randomized cross-over design, 16 individuals underwent two sessions of a-tDCS and two sham tDCS (s-tDCS) sessions, with testing of either the left or right quadriceps. Maximal knee extensor force was recorded prior to and following the a-tDCS and s-tDCS protocols. Additionally, a repetitive maximal force fatigue protocol was completed following each tDCS protocol. The main finding of this study was that there was a significant reduction in absolute and relative maximal force of the left (ipsilateral to a-tDCS) quadriceps following a-tDCS but not the sham session. There were no significant differences in maximal force found for the right quadriceps (contralateral to tDCS). Additionally, no significant differences in fatigue endurance were found for either the quadriceps of either limb. This work demonstrates that a-tDCS may be ineffective at increasing exercise performance and instead may be detrimental to the muscles' ability to produce force. There were no observed differences in maximal force production or fatigue endurance between the sexes which suggests both male and female participants are affected by a-tDCS to a similar extent.

Keywords: tDCS, Performance, Endurance, Strength, Fatigue

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate cortical excitability (Nitsche & Paulus, 2000). tDCS can induce both excitatory and inhibitory effects depending on the polarity of the stimulation administered (Nitsche & Paulus, 2000). tDCS for clinical use has been investigated involving the treatment of depression, anxiety, schizophrenia, Parkinson's disease, chronic pain, and other neural-related problems (Alonzo et al., 2013; Fang & Wang, 2021; Brunelin et al., 2012; Pereira et al., 2013; Treister et al., 2015). Additionally, many studies have demonstrated that tDCS is effective at increasing maximal muscle force production and muscle endurance (Tanaka et al., 2009; Krishnan et al., 2014; Frazer et al., 2016; Sales et al., 2016; Lattari et al., 2018; Lattari et al., 2020a; Okano et al., 2015; Hazime et al., 2017; Vargas et al., 2018, Angius et al., 2016; Angius et al., 2018; Vitor-Costa et al., 2015; Cogiamanian et al., 2007; Park et al., 2019; Abdelmoula et al., 2016; Williams et al., 2013; Lattari et al., 2016; Lattari et al., 2020b; Oki et al., 2016). However, many others report no significant effects on muscle force production or endurance (Kan et al., 2013; Montenegro et al., 2015; Cogamanian et al., 2007; Giboin & Gruber 2018; Abdelmoula et al., 2016; Lampropoulou & Nowicky, 2013, Angius et al., 2016; Barwood et al., 2016; Angius et al., 2015; Flood et al., 2017; Kan et al., 2013; Radel et al., 2017; Montenegro et al., 2015; Sasada et al, 2017; Muthalib et al., 2013).

There are many variables that can influence the administration and effectiveness of tDCS. It has previously been estimated that when accounting for electrode location, size, number, current density, polarity, and stimulation duration, there are between four million to eight trillion individual protocols that can be implemented (Machado et al., 2019). Although, for studies that are interested in the modulation of muscle force production and fatigue endurance, the majority

use the motor cortex (M1) contralateral to the muscles of interest as the targeted area for stimulation, while some have also targeted the temporal cortex and the prefrontal cortex (Machado et al., 2019). Although, only one study up to this point has investigated the effect that tDCS of the M1 can have on muscles ipsilateral to the site of stimulation (Vargas et al., 2018).

Phenomenon such as cross-education have provided insight on the crosstalk between hemispheres during exercise. Several studies utilizing transcranial magnetic stimulation (TMS) have found that the M1 ipsilateral to trained muscles plays an important role in the facilitation of cross education in muscle groups (Goodwill et al., 2012; Kidgell et al., 2011; Mason et al., 2018; Hortobágyi et al., 2011). These studies found that following training of a muscle group, there were increases in the excitability of the ipsilateral M1 for the homologous muscle, along with decreases in intracortical inhibition (Goodwill et al., 2012; Kidgell et al., 2011; Mason et al., 2018; Hortobágyi et al., 2011). Therefore, it may be possible that a similar mechanism allows for anodal tDCS (a-tDCS) induced increases in neural drive to spillover into the contralateral M1. This could result in performance enhancements in muscles ipsilateral to the site of stimulation. Studies have also found evidence of interhemispheric facilitation of the motor cortices using sub-motor-threshold intensity TMS stimulation which suggests the existence of an underlying faciliatory neuronal circuit (Bäumer et al., 2006; Hanajima et al., 2001). This is done by giving a sub-threshold conditioning TMS pulse to one of the motor cortices, followed by a test pulse to the contralateral M1. While faciliatory effects were present, it should be noted that they are usually found between 4-8 milliseconds following the conditioning pulse (Bäumer et al., 2006). One study using a single pulse supra-threshold TMS design demonstrated that a-tDCS could increase excitability of the contralateral motor cortex (Zhao et al., 2015). This study examined the motor cortex responsible for swallowing, where contralateral muscles must work

synergistically, so it is unclear if a similar effect would be seen in non-synergistic contralateral muscles (Zhao et al., 2015).

It is also possible that uncrossed corticospinal fibres that target ipsilateral motor neurones and branched corticospinal fibres projecting to motor neurones bilaterally are affected. Although, this is less likely since these projections are strongest to axial muscles and may not be present for distal limb muscles (Carroll et al., 2006). Other potential mechanisms of performance improvements in muscles ipsilateral to the stimulated site include the possibility that the ipsilaterally descending reticulospinal system is impacted, as has been shown in non-human animal models (Bolzoni et al., 2013; Bączyk et al., 2014) or potential effects on mirror neurones (Enticott et al., 2012).

While Vargas et al. (2018) reported no changes in maximal force production if the knee extensors following tDCS of the ipsilateral M1, no studies thus far have tested whether stimulation can affect fatigue in muscles ipsilateral to the site of stimulation. Therefore, the main goal of this study was to determine whether unihemispheric a-tDCS of the M1 is capable of modulating maximal force production or fatiguability of the either the contralateral and ipsilateral knee extensors (KE). Additionally, sex differences were analyzed to possible sex-specific effects of tDCS.

Research Questions

1. Will a-tDCS to the motor cortex affect maximal force production or fatigue resistance in the contralateral or ipsilateral KE?

   It is hypothesized that there will be an increase in maximal force production and fatigue resistance in the contralateral, but not ipsilateral, KE in relation to the site of tDCS.
2. Will a-tDCS affect male and female participants to a similar extent?

It is difficult to form a hypothesis based on the lack of literature surrounding sex dependent effects of a-tDCS. Therefore, this research question is considered exploratory.

Methods

Participants

A priori power analyses (software package, G* Power 3.1.9.7: University of Dusseldorf, Germany) conducted using the results from studies by Hazime et al. (2017) and Lattari et al. (2020a) suggested a required sample size of 10 and 8, respectively. Therefore, 16 healthy, participants were recruited for this study (8 males; age = 24.1 ± 2.8 years, height = 173.2 ± 8.3 cm, mass = 86.1 ± 13.3 kg and 8 Females; age = 21.9 ± 1.6 years, height = 163.2 ± 8.6 cm, mass = 70.0 ± 14.7 kg). Participants were recreationally active with no history of musculoskeletal disorders and were screened for their suitability to receive tDCS based on recommendations by Thair et al. (2017). Participants were asked "which leg they would use to kick a ball at a target" to determine lower limb dominance (Melick et al., 2017). All participants were determined to be right leg dominant. Each participant was required to read and sign a consent form prior to participation in the study. This study was approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR No. 20201316-HK).

Experimental Design

This study utilized a fully randomized, repeated measures design, with all participants completing four protocols. The four protocols involved: 1) the participant receiving a-tDCS to the left M1, with testing of the contralateral (right) leg, 2) the participant receiving a-tDCS to the left M1 with testing of the ipsilateral (left) leg, 3) the participant receiving sham tDCS (s-tDCS) to the left M1, with testing of the contralateral (right) leg, and 4) the participant receiving s-tDCS to the left M1 with testing of the ipsilateral (left) leg.

tDCS Intervention

Participants underwent four sessions of tDCS (two a-tDCS and two s-tDCS) delivered via a direct current stimulator (TCT Research Limited, Hong Kong) using saline-soaked sponge electrodes. For all sessions, the anode (5 x 5cm) was placed at the left M1, contralateral to the participant's dominant limb, with the cathode (5 x 7cm) placed on the shoulder area of the same side (Cogiamanian et al., 2007; Abdelmoula et al., 2016; Lampropoulou & Nowicky, 2013). The M1 was located via the C3/C4 locations according to the 10-20 electrode placement system (Hazime et al., 2017; Vargas et al., 2018; Montenegro et al., 2015). a-tDCS protocols had a constant stimulation intensity of 2 milliamps (mA) with a duration of 10 minutes (Kan et al., 2013; Angius et al., 2016; Angius et al., 2015). The s-tDCS protocols involved participants receiving 2 mA stimulation for the initial 30 seconds, followed by an additional 9.5 minutes of no stimulation (Angius et al., 2016).

MVC and Fatigue Tests

Prior to any performance measurements, participants completed a five-minute warm up using a cycle ergometer at 70 revolutions per minute and 1 kilopond.

To measure force, a cuff with a non-extensible strap was attached to a strain gauge (Omega Engineering Inc., LCCA 500 pounds; sensitivity = 3 mV/V, OEI, Canada) and placed around the ankle of the participant. Knee joint angles were measured using a goniometer, since it has previously been shown that knee angle can affect maximal voluntary contraction force (MVC) (Papadopoulos et al., 2008). Before KE and knee flexor (KF) maximal voluntary contractions, participants were instructed to complete three warm-up contractions at what they perceived to be 50% of their maximum capability for five seconds each. Prior to each tDCS protocol, participants performed a minimum of two four second MVCs for both the left and right

KE and KF, with a third MVC completed if the second MVC resulted in more than a five percent greater force than the initial contraction. Participants were instructed to contract "as hard and as fast as possible", with verbal encouragement being provided during the contractions (Caldwell et al., 2019). The testing order of these muscle groups was randomized for each participant session. Immediately post-tDCS protocol, participants performed a single KE MVC of either the left or right KE. Only a single MVC was performed to minimize the effect on the following fatigue protocol. Peak MVC forces were analyzed for the KE of the tested leg. KF MVCs were conducted during the pre-test only for the purposes of electromyography (EMG) normalization, thus no post-test contractions of the KF were completed. Pre-tDCS KE contractions were also used for EMG normalization in addition to the analysis of force. All force data was sampled at 2000 Hz and analyzed with the software program (AcqKnowledge III, Biopac Systems Inc., Holliston, MA).

Following the post-tDCS MVC, participants performed a repeated contraction (fatigue) protocol consisting of 12 MVCs with a work to rest ratio of 5:10 seconds (Halperin et al., (2014a). During this protocol, participants were not told how many contractions had been completed in order to minimize pacing effects (Reid et al., 2017; Halperin et al., 2014b; Halperin et al., 2014c). All participants were similarly verbally exhorted to maximize each contraction (Halperin et al., 2020). A fatigue index (Equation 1) was calculated and analyzed.

$$Fatigue\ index = \frac{Mean\ force\ of\ repetitions\ 11\ \&\ 12}{Mean\ force\ of\ repetitions\ 1\ \&\ 2}/100$$

Equation 1: Fatigue index calculation

Electromyography (EMG)

EMG activity was recorded during all single, discrete MVCs and 12 repetition fatigue tests. The skin was prepared for surface electrode placement by shaving, abrading, and cleaning with an alcohol swab. Two self adhesive 3.2 centimetre diameter Ag/AgCl electrodes (Meditrace TM 130 ECG conductive adhesive electrodes) with an edge-to-edge inter electrode spacing of 20 millimetres were used per recorded muscle. Electrodes were taped down to prevent movement during testing. The electrodes were placed over the biceps femoris and vastus lateralis in accordance with the SENIAM recommendations (Hermens et al., 2000).

EMG activity was amplified (x1000) (Biopac Systems Inc., DA100; analog-digital converter MP150WSW, Holliston, MA). The root mean square (RMS) EMG was analyzed. The data was sampled at 2000 Hz and analyzed with the software program (AcqKnowledge III, Biopac Systems Inc., Holliston, MA). EMG was normalized to the highest force pre-test MVC EMG.

Supplementary tDCS Questionnaire

Before and after receiving tDCS (either a-tDCS or s-tDCS), participants were given a questionnaire (Appendix 1), where they were asked to rate perceived sensations (e.g., itching, tingling, anxiety) on a scale from 1-10 (Likert scale: 1 = absent, 10 = severe) (Thair et al., 2017).

Statistical Analysis

Statistical analyses were calculated using SPSS software (Version 27.0, SPSS, Inc. Chicago, IL). Normality and homogeneity of variances tests were conducted for all dependent variables. If the assumption of sphericity was violated, the Greenhouse-Geiser correction was employed. For absolute MVC force, a four-way repeated measures ANOVA (2x2x2x2) with factors including sex, time (pre/post tDCS), tDCS protocol (anodal/sham), and tested leg (left

(ipsilateral to tDCS)/right (contralateral to tDCS)) was conducted. For the fatigue index and normalized EMG (equation 2), a three-way repeated measures ANOVA (2x2x2) with factors including sex, condition, and leg tested was also completed. The three-way repeated measures ANOVA (2 sexes x 2 conditions x 2 legs) was conducted since significant absolute force differences between sexes were documented with the 4-way ANOVA, which would have contributed to increased data variance. In addition, the multiple factors in a four-way ANOVA also makes it difficult to ascertain statistically meaningful differences with 16 participants. Hence, further analysis involved normalizing the post-test tDCS MVC forces to the pre-test tDCS values for each participant (Equation 2).

$$MVC\ Force\ and\ EMG\ Normalization = \frac{Post - tDCS}{Pre - tDCS}\ x\ 100\%$$

Equation 2: MVC Force and EMG normalization calculation.

Post-hoc t-tests were conducted to determine differences between values. Intraclass correlation coefficients were measured for the pre-test trials of each condition to assess the consistency of the data. Significance was set at $p \leq 0.05$. Cohen's *d* effect size was calculated to compare measures.

Friedman's ANOVA was utilized to detect significant main effects and interactions for scales related to headache, neck pain, blurred vision, scalp irritation, tingling, itching, burning sensation, acute mood change, fatigue, and anxiety. For significant effects post-hoc Wilcoxon Signed Ranks and Mann Whitney U tests were performed.

Day to day reliability for pre-test MVC was assessed with Cronbach's alpha intraclass correlation coefficient (ICC).

Results

Absolute Force Measures

An excellent degree of reliability was found between pre-test measurements for the right ($\alpha = 0.943$) and left ($\alpha = 0.964$) KE.

There was a significant [$F(1,56) = 66.58$, $p < 0.001$)] main effect for time with a moderate magnitude 8.7% ($d = 0.75$) decrease in tested KE MVC from pre to post test, with no significant interaction effects found for sex (sex x time), condition (condition x time), or leg tested (leg tested x time).

There were no interaction effects found for sex and condition (sex x condition x time), sex and tested limb (sex x leg tested x time), or sex, condition, and tested limb (sex x condition x tested leg x time). A significant main effect for sex was revealed [$F(1,56) = 66.58$, $p < 0.001$], showing a mean sex difference of 234.8 N and 214.1 N in pre- [$t(44.47) = 8.793$, $p < 0.001$, $d = 2.20$] and post-test [$t(41.23) = 7.759$, $p < 0.001$, $d = 1.94$] maximal force production, respectively.

A significant [$F(1,56) = 6.98$, $p = 0.011$] interaction effect was found for condition and leg tested (condition x leg tested x time). Participants' maximal left (ipsilateral to tDCS) KE force was reduced by 14% following a-tDCS when compared to the pre-stimulation values [$t(15) = 4.35$, $p = 0.001$, $d = 1.09$], but no significant change for s-tDCS. There were also significant [$t(15) = 4.84$, $p < 0.001$, d =1.21] and near significant [$p = 0.057$, $d = 0.52$] force reductions of 10.7% and 5.7% in the right (contralateral to tDCS) following the s-tDCS and a-tDCS protocols, respectively (Table 1).

Table 1: Average participant absolute knee extensor force sorted by leg tested and stimulation received. (* denotes statistical significance at $p \leq 0.05$)

Leg Tested	tDCS	Pre-test Mean ± SD (N)	Post-test Mean ± SD (N)	*p*
Right (Contralateral to tDCS)	Anodal	476.4 ± 150.7	449.4 ± 145.3	0.057
	Sham	489.5 ±149.4	437.2 ± 134.6	0.001*
Left (Ipsilateral to tDCS)	Anodal	479.7 ± 174.9	412.3 ±171.0	< 0.001*
	Sham	480.4 ± 173.8	459.6 ± 171.5	0.156

Relative (normalized) MVC Force

A significant interaction effect for condition x leg tested [$F(1,56) = 8.12$, $p = 0.006$], showed a significantly lower left quadriceps (ipsilateral to tDCS) relative MVC force with a-tDCS (85.92 ± 12.75 %), versus s-tDCS (106.19 ± 15.76 %) [$t(15) = -3.01$, $p = 0.009$, $d = -0.75$]. There was no significant difference between the relative right quadriceps (contralateral to tDCS) MVC force for a-tDCS and s-tDCS (Figure 1).

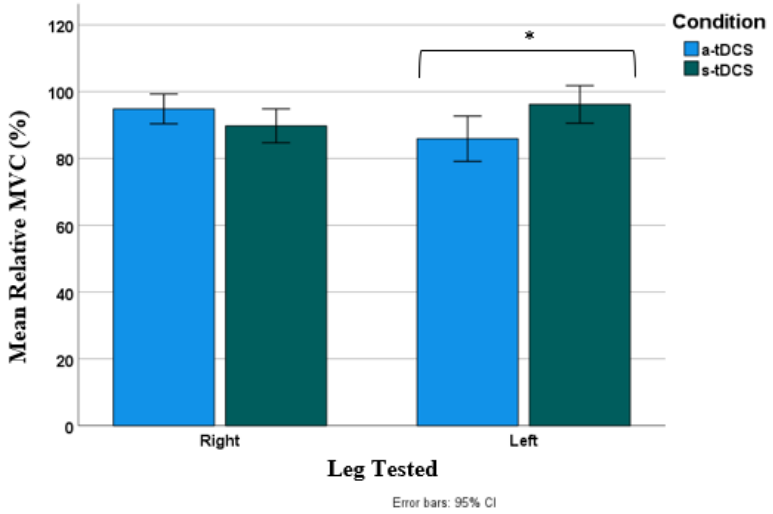

Figure 1: Grouped (n = 16) Mean relative quadriceps MVC force grouped by leg tested and condition. (* denotes a statistically significant difference between groups $p \leq 0.05$)

Relative (normalized) EMG data

Post-tDCS RMS EMG revealed significant interactions for condition x leg tested [$F(1,53) = 6.65$, $p = 0.013$] and sex x leg tested [$F(1,53) = 4.23$, $p = 0.045$]. Normalized EMG was significantly and near significantly lower in the left (ipsilateral to tDCS) [$t(14) = -4.04$, $p = 0.001$, $d = -1.04$] and right (contralateral to tDCS) [$t(13) = 2.144$, $p = 0.052$, $d = 0.57$] vastus lateralis, respectively following a-tDCS than following s-tDCS (Table 2). There was an 8.2 % significantly lower normalized EMG of the right vastus lateralis following s-tDCS than in the left vastus lateralis [$t(13) = -2.43$, $p = 0.030$, $d = -1.22$] (Table 3). The right quadriceps of male participants (87.3 ± 12.0%) also exhibited 11.8 % lower average normalized EMG regardless of tDCS compared to female participants (99.1 ± 15.8%) [$t(29) = -2.33$, $p = 0.027$, $d = 0.84$], while there was no significant difference for the left quadriceps. Additionally, female participants exhibited a 9.4% higher average normalized EMG in their right quadriceps (99.5 ± 16.3 %) than their left quadriceps (90.11 ± 15.8 %), irrespective of tDCS [$t(14) = 5.96$, $p < 0.001$, $d = 1.54$].

Table 2: Average normalized vastus lateralis EMG for a-tDCS and s-tDCS separated by leg tested. (* denotes statistical significance at $p \leq 0.05$)

Leg Tested	**a-tDCS Mean ± SD (%)**	**s-tDCS Mean ± SD (%)**	**p**
Right (Contralateral to tDCS)	96.7 ± 15.0	86.9 ± 12.8	0.052
Left (Ipsilateral to tDCS)	84.2 ± 21.6	101.8 ± 19.0	0.001*

Table 3: Average normalized vastus lateralis EMG for right and left legs separated by tDCS condition (* denotes statistical significance at $p \leq 0.05$)

tDCS	**Right Leg Mean ± SD (%)**	**Left Leg Mean ± SD (%)**	**p**
Anodal	97.4 ± 14.8	86.0 ± 12.9	0.078
Sham	87.1 ± 12.9	102.8 ± 19.3	0.030*

During the pre-tDCS contractions, the vastus lateralis and biceps femoris of the non-tested, resting leg showed a mean EMG of 4.4 ± 3.9 %, and 11.6 ± 10.3 %, of MVC respectively. During the post-tDCS contractions, the vastus lateralis and biceps femoris of the relaxed, resting leg showed an average EMG of 3.4 ± 2.7 %, and 11.15 ± 12.93 % of MVC, respectively. The tested leg biceps femoris (antagonist during quadriceps MVC) demonstrated EMG activity of 23.6 ± 14.7 % and 23.0 ± 15.2 % of MVC with pre-test and post-test, respectively.

Fatigue Index

A three-way repeated measures ANOVA (2x2x2) revealed no significant main or interaction effects for fatigue index force.

Table 4: Fatigue index force for the right and left KE (* denotes statistical significance at $p \leq 0.05$)

Leg Tested	**s-tDCS Mean ± SD**	**a-tDCS Mean ± SD**	**p**
Right KE	86.7 ± 12.2	86.8 ± 10.3	0.974
Left KE	89.3 ± 9.7	89.0± 9.3	0.934

Questionnaire Data

Friedman's ANOVA revealed significant main effects for time for scalp irritation [$X^2_F(1) = 24.00$, $p < 0.001$], tingling [$X^2_F(1) = 27.00$, $p < 0.001$], itching [$X^2_F(1) = 32.00$, $p < 0.001$], and burning sensation [$X^2_F(1) = 5.00$, $p = 0.025$].

Both males and females reported significantly increased levels of scalp irritation (males [$T = 105$, $z = -3.41$, $p = 0.001$] and females [$T = 55$, $z = -2.913$, $p = 0.004$]), tingling (males [$T = 153$, $z = -3.82$, $p < 0.001$] and females [$T = 55$, $z = -2.88$, $p = 0.004$]) and itching (males [$T =$

190, z = -4.01, $p < 0.001$] and females [T = 91, z = -3.30, p = 0.001]) following tDCS overall (sham and anodal combined).

Comparing a-tDCS and s-tDCS overall, scalp irritation, tingling, and itching were significantly increased following both a-tDCS (scalp irritation: [T=136, z = -3.66, $p < 0.001$], tingling: [T=190, z = -4.02, $p < 0.001$] and itching: [T=253, z = -4.35, $p < 0.001$]) and s-tDCS (scalp irritation: [T = 36, z = -2.59, p = 0.010], tingling: [T = 36, z = -2.59, p = 0.010], and itching: [T = 55, z = -2.87, p = 0.004]). Participants reported significantly higher levels of scalp irritation [T = 28, z = -1.968, p = 0.049], tingling [T = 40, z = -2.128, p = 0.033] and itching [T = 28, z = -2.42, p = 0.015] following a-tDCS in comparison to s-tDCS.

Regarding sex differences, both male and female participants reported increased scalp irritation (male [T = 55, z = -2.88, p = 0.004] and female [T = 21, z = -2.33, p = 0.020]), tingling (male [T = 78, z = -3.21, p = 0.001] and female [T = 28, z = -2.46, p = 0.014]), and itching (male [T = 91, z = -3.35, p = 0.001] and female [T = 45, z = -2.81, p = 0.005]) following a-tDCS. Male participants also reported an average increase in tingling [T = 15, z = -2.12, p = 0.034] and itching [T = 21, z = -2.26, p = 0.024] following s-tDCS while females reported no significant change. Scalp irritation following s-tDCS did not reach statistical significance for either sex (Table 4). There was no significant difference between male and female tingling or itching scores before or after a-tDCS or s-tDCS.

Table 5: Median questionnaire variable ratings before and after tDCS (* denotes statistical significance at $p \leq 0.05$)

tDCS		Sex	Pre-test Median	Post-test Median	*p*
Anodal	Scalp Irritation	Male	1	2	0.004*
		Female	1	1	0.020*
	Tingling	Male	1	2	0.001*
		Female	1	1	0.014*
	Itching	Male	1	2	0.001*
		Female	1	2	0.005*
Sham	Scalp Irritation	Male	1	1	0.059
		Female	1	1	0.066
	Tingling	Male	1	1	0.034*
		Female	1	1	0.109
	Itching	Male	1	1	0.024*
		Female	1	1	0.066

Post-hoc tests did not reveal any significant interactions for levels of burning sensation.

Discussion

The main objective of this study was to determine if a-tDCS of the left M1 could modulate maximal force production or muscle fatiguability in either the right (contralateral to tDCS) or left (ipsilateral to tDCS) quadriceps. Unlike Vargas et al. (2018), who reported no significant changes in quadriceps MVC force of participants who received a-tDCS ipsilateral to the M1, our study found both a significantly greater absolute and relative decrease MVC force of

the ipsilateral (left) KE following a-tDCS when compared to the pre-test values, and sham protocol, respectively. To our knowledge, this is the first study to demonstrate a significant decrease in force for a discrete (single repetition) MVC following a-tDCS for muscles either contralateral or ipsilateral to the site of stimulation.

This decrease in relative force was accompanied by an average reduction in normalized EMG activation of the ipsilateral (left) vastus lateralis following a-tDCS in comparison to s-tDCS. Giboin & Gruber (2018) found decreased MVC force of the KE contralateral to the anodally stimulated M1 during an intermittent maximal effort fatigue task, although there was no significant effect on the first MVC completed. It may be possible that the mechanism responsible for the decrease in maximal force production ipsilateral to the stimulated M1 is related to intercortical neuronal circuits, such as those responsible for interhemispheric inhibition (IHI). These circuits have been shown to allow the left and right M1 to send inhibitory impulses to one another, which has previously been shown, using TMS, to modulate the motor output of both proximal (Harris-Love et al., 2007) and distal (Ferbert et al., 1992; Harris-Love et al., 2007) upper limb muscles. IHI effects on muscles of the lower limb have been investigated less extensively, due in large part to how close the location of lower limb representations of the M1 are anatomically (Hendy et al., 2017). A previous study, which investigated the effect of tDCS on IHI found that following a-tDCS of the right M1, IHI from the stimulated M1 to the non-stimulated M1 was increased (Tazoe et al., 2014). While this study also reported an increased excitability in the stimulated M1, no change in the non-stimulated M1 excitability was found (Tazoe et al., 2014). It may be possible that the observed decrease in MVC force in the quadriceps ipsilateral to the site of stimulation is related to an increase in IHI from the stimulated M1 to the contralateral M1. Since we did not measure IHI, this distinction cannot be ascertained.

Additionally, since we did not use TMS to measure corticospinal excitability either before or after stimulation, we cannot be certain if the reduction in observed force was accompanied by a change in excitability of the non-stimulated M1. While corticospinal excitability was not measured, there was significant reduction in normalized EMG following a-tDCS in comparison to s-tDCS suggests a significant decrease in voluntary activation of the muscle. It may also be possible that the decreased force of the ipsilateral KE is a result of an a-tDCS induced decreased interhemispheric facilitation, however there is little evidence to support this possibility.

The hypothesized a-tDCS induced increase in M1 excitability leading to increased MVC force of the KE was not observed. The lack of significant change in normalized MVC force of the right KE (contralateral to tDCS) following a-tDCS, in comparison to s-tDCS was contradictory to many studies which have reported force increases following anodal stimulation of the M1 (Tanaka et al., 2009, Krishnan et al., 2014; Frazer et al., 2016; Hazime et al., 2017; Vargas et al., 2018). Although only one of the studies that reported increases, tested the KE (Vargas et al., 2018), while a larger number of studies testing the KE following a-tDCS reported no significant changes in comparison to the control (Montenegro et al., 2015; Giboin & Gruber et al., 2018; Flood et al., 2017; Angius et al., 2016; Washabaugh et al., 2016). The results of this study, in combination with previous research suggests that a-tDCS is not an effective ergogenic aid when the goal is to increase maximal KE force for a discrete contraction.

The anodal and sham tDCS post-test protocols were conducted after approximately 10 minutes of physical inactivity. While the pre-test MVCs were performed shortly after a warm-up, the beneficial effects of this warm-up may have subsided after 10 minutes of inactivity (Behm et al. 2016; Behm et al., 2021). The reported force losses might be attributed to a diminished warm-up induced post-activation potentiation enhancement that can increase force through

phosphorylation of myosin light chains, and increased muscle temperature (Blazevich & Babault, 2019). However, there are previous tDCS studies that reported improved force output that involve participants completing MVCs after a prolonged period in a rested state (Vargas et al., 2018; Tanaka et al., 2009). Nevertheless, it is also possible that the decrease in MVC force in the ipsilateral KE following a-tDCS is due to a loss of warm-up benefits, while the non-significant difference in MVC force following a-tDCS in the contralateral KE is due to a tDCS induced increase in M1 excitability, which counterbalanced and diminished the warm-up potentiation effects.

With a-tDCS showing the ability to increase M1 excitability, it has been hypothesized that a-tDCS could attenuate the reduction in output from the M1 contributing to supraspinal fatigue (Nitsche & Paulus 2001; Angius et al., 2016). It has previously been demonstrated that a-tDCS can delay the onset of fatigue for a prolonged submaximal contraction (Oki et al., 2016; Williams et al., 2013; Angius et al., 2016; Cogiamanian et al., 2007), although again, only one of these studies tested the KE (Angius et al., 2016). Numerous other studies also reported no significant changes in KE fatiguability following a-tDCS (Angius et al., 2016; Flood et al., 2017; Kan et al., 2013) with one study also reporting increased muscle fatiguability (Giboin & Gruber, 2018). While Angius et al. (2016) suggested an extracephalic electrode montage was more effective at inducing a-tDCS effects on muscle fatigue than cephalic montages, our study used a nearly identical extracephalic protocol and found contrasting results. It is possible that the difference in fatigue test used may have led to this discrepancy, with our study utilizing a 12 x 5s MVC protocol while Angius et al. (2016) utilized a submaximal 20% MVC force time to exhaustion test. This suggests that a-tDCS is more effective for delaying the effect of muscle

fatigue for low intensity activities, while those requiring maximal exertions will not experience the same benefits.

This study found no significant differences between male and female participants for relative force production or fatigue index. This suggests that tDCS affects male and female participants to a similar extent. A previous study did report that the effects of cathodal tDCS were greater and lasted longer for female participants in comparison to males, suggesting that female participants may experience increased effects of tDCS when compared to males (Kuo et al., 2006). Although, this same study did not report significant differences between the sexes for a-tDCS (Kuo et al., 2006). Our findings suggest that a-tDCS has similar performance effects for both male and female participants. Although, since we did not utilize cathodal stimulation in this study, future work should compare the effects of cathodal tDCS on exercise performance between sexes.

Female participants had a significantly higher relative activation in the right vastus lateralis following either sham or anodal tDCS than male participants, although there was no significant difference for the left vastus lateralis.

Gandiga et al. (2005) previously reported that a-tDCS and s-tDCS protocols produced comparable sensations of discomfort and duration, and those participants were not able to accurately distinguish between tDCS and sham protocols, thereby making 30 seconds of stimulation followed by no stimulation for a set duration an effective control for single and double-blind procedures. This study found significantly higher levels of scalp irritation, tingling, and itching following both a-tDCS and s-tDCS in comparison to the pre-test. Additionally, the ratings of these variables were all significantly higher following a-tDCS when compared to s-tDCS, suggesting participants may be able to differentiate between the protocols. Although,

since the overall ratings of these variables for participants were low, this significant difference may not be meaningful enough for participants to accurately differentiate the protocols. Moreover, since our study did not poll participants regarding whether they believed if they had received a-tDCS versus the sham, it cannot be said for certain whether 30 seconds of stimulation was an effective blinding protocol in this study. It would be of interest of future studies to use additional measures, such as polling participants on whether they believed they received tDCS or the sham to help determine the true effectiveness of 30 seconds of stimulation for blinding of tDCS protocols.

Conclusion

This study found that 10 minutes of 2 mA of a-tDCS is not an effective method for increasing maximal force production or reducing fatigue in the KE either contralateral or ipsilateral to the stimulated M1. In fact, a-tDCS to the M1 can have detrimental effects on maximal voluntary isometric force in the ipsilateral KE. Additionally, following a-tDCS 5/16 (2 males, 3 females) and 1/16 (1 female) participants reported increased MVC force in their right and left quadriceps, respectively. This adds to the growing body of literature that tDCS is not a reliable ergogenic aid since the effects can be highly variable. With many athletes looking to devices such as those for administering tDCS to provide performance enhancements, it is important to caution that tDCS may not be beneficial but could instead be detrimental to exercise performance. Future studies should aim to determine if other muscle groups ipsilateral to the site of stimulation are affected in a similar manner, while also utilizing TMS to determine potential changes in M1 excitability and IHI. Studies should also implement procedures to help determine the effectiveness of a 30s s-tDCS protocol as a blinding protocol and attempt to discern if c-tDCS affects male and female participants exercise performance measures to varying extents.

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Chapter 4: Summary & Future Directions

With substantial conflict in the literature as to whether transcranial direct current stimulation (tDCS) can act as an effective performance aid, this thesis research adds to the growing body suggesting that anodal tDCS (a-tDCS) cannot improve maximal force production or fatigue endurance. This research is also the first to find performance decrements in muscles ipsilateral to the stimulated motor cortex. As many professional athletes look to devices such as those used for tDCS to gain an edge in performance, more research needs to be done to determine exactly how tDCS affects muscular performance throughout the body. Future studies should attempt to determine if a-tDCS can result in performance decrements in other muscle groups ipsilateral to the site of stimulation, as observed in the knee extensors during this research. Additionally, these studies should implement the use of transcranial magnetic stimulation to measure both cortical excitability in the non-stimulated motor cortex, and interhemispheric inhibition sent from the stimulated cortex. This work would give further insight into how exactly tDCS caused decrements in maximal force production in the ipsilateral knee extensors.

This research reported no significant differences between male and female participants for relative force or fatigue index following a-tDCS, suggesting that anodal stimulation affects male and female participants to a similar extent. Although, since cathodal tDCS was not utilized, it would be of interest of future studies to determine if this reversed polarity tDCS also affects muscle performance for both sexes to a comparable degree.

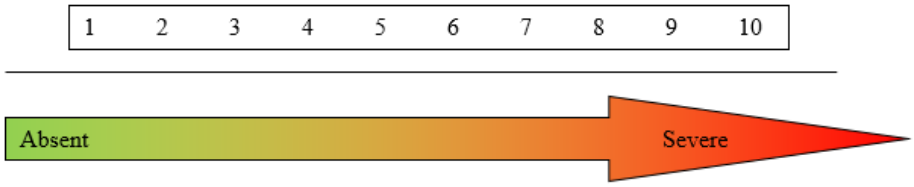
Finally, with the above research raising questions as to whether 30 seconds of tDCS is an effective blinding protocol, future studies should implement questionnaires/polls to determine whether participants can accurately differentiate true tDCS from the sham protocol. Specifically,

participants should be asked after each session, whether they believed if they received the active or sham condition. If it is found that the current sham protocol is ineffective, researchers should attempt to find an alternative which can help to eliminate participant bias.

Appendix A: Supplementary tDCS Questionnaire

SUPPLEMENTARY MATERIAL A: tDCS experiment questionnaire

This questionnaire will be filled in before and after receiving tDCS. Please enter a value from 1-10, ranging from absent to severe, in the 'Rating' space below in response to the question: "Do any of these statements currently apply to you?" It is important that you answer all questions truthfully.



Do any of these statements currently apply to you?	Rating		Notes
	Before tDCS	**After** tDCS	
1. Headache			
2. Neck pain			
3. Back pain			
4. Blurred vision			
5. Scalp irritation			
6. Tingling			
7. Itching			
8. Increased heart rate			
9. Burning sensation			

10. Hot flush			
11. Dizziness			
12. Acute mood change			
13. Fatigue			
14. Anxiety			
Others:			

Instructions for application

Before: If participants score '5' or above for any of the statements*, they should not participate on the day. This is for their own safety and comfort as tDCS has been shown to temporarily aggravate some of these conditions.

After: If participants have scored '5' or above for any of the statements*, they should stay in the laboratory until symptoms have subsided or until they and the researcher are satisfied for them to leave. If their symptoms persist for more than 24 hours then the researcher should be contacted and appropriate medical attention should be sought.

*Apart from questions 3, 8, 10 and 11 as these are pseudo items

Appendix B: Ethical Approval

MEMORIAL UNIVERSITY

Interdisciplinary Committee on
Ethics in Human Research (ICEHR)

St. John's, NL Canada A1C 5S7
Tel: 709 864-2561 icehr@mun.ca
www.mun.ca/research/ethics/humans/icehr

ICEHR Number:	**20201316-HK**
Approval Period:	January 13, 2020 – January 31, 2022
Funding Source:	NSERC [RGCS# 20171793; Behm]
Responsible Faculty:	Dr. David Behm School of Human Kinetics and Recreation
Title of Project:	*The effects of tDCS on hip joint range of motion, hamstrings force output, and endurance*
Amendment #:	***02***

May 12, 2021

Mr. Ryan Savoury
School of Human Kinetics and Recreation
Memorial University of Newfoundland

Dear Mr. Savoury:

The Interdisciplinary Committee on Ethics in Human Research (ICEHR) has reviewed the proposed modifications for the above referenced project, as outlined in your amendment request dated April 20, 2021, and is pleased to give approval to the revised protocols, as described in your request and subsequent communication, provided all other previously approved protocols are followed.

The *TCPS2* **requires** that you **strictly adhere to the protocol and documents as last reviewed** by ICEHR. If you need to make any other additions and/or modifications during the conduct of the research, you must submit an Amendment Request with a description of these changes, for the Committee's review of potential ethical issues, before they may be implemented. Submit a Personnel Change Form to add or remove project team members and/or research staff. Also, to inform ICEHR of any unanticipated occurrences, an Adverse Event Report must be submitted with an indication of how the unexpected event may affect the continuation of the project.

Your ethics clearance for this project expires **January 31, 2022**, before which time you must submit an Annual Update to ICEHR, as required by the *TCPS2*. If you plan to continue the project, you need to request renewal of your ethics clearance, and include a brief summary on the progress of your research. When the project no longer requires contact with human participants, is completed and/or terminated, you need to provide an annual update with a brief final summary, and your file will be closed.

All post-approval ICEHR event forms noted above must be submitted by selecting the *Applications: Post-Review* link on your Researcher Portal homepage.

The Committee would like to thank you for the update on your proposal and we wish you well with your research.

Yours sincerely,

Kelly Blidook, Ph.D.
Vice-Chair, Interdisciplinary Committee on
Ethics in Human Research

KB/bc

cc: Supervisor – Dr. David Behm, School of Human Kinetics and Recreation