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TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE DORSOLATERAL PREFRONTAL CORTEXT DOES NOT IMPROVE HANDGRIP TIME-TO-FAILURE OR ALTER CENTRAL OR PERIPHERAL HEMODYNAMICS

By

Yousef Qadumi

THESIS

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TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE DORSOLATERAL PREFRONTAL CORTEXT DOES NOT IMPROVE HANDGRIP TIME-TO-FAILURE OR ALTER CENTRAL OR PERIPHERAL HEMODYNAMICS

This thesis by Yousef Qadumi is recommended for approval by the student's Thesis Committee and Department Head in the School of Health and Human Performance and by the Dean of Graduate Studies and Research.

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ABSTRACT

TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE DORSOLATERAL PREFRONTAL CORTEXT DOES NOT IMPROVE HANDGRIP TIME-TO-FAILURE OR ALTER CENTRAL OR PERIPHERAL HEMODYNAMICS

By

Yousef Qadumi

Age-related deviations to the neuromuscular system negatively impact motor function and performance. Transcranial direct current stimulation (tDCS) has been linked to improvements in the neuromuscular system. The purpose of this study was to determine if tDCS delivered to the dorsolateral prefrontal cortex (DLPFC) would improve handgrip time-to-failure in adults 60 years old and older. Twenty-five participants completed five maximal voluntary contractions, followed by 20-minutes of a-tDCS or SHAM conditions. Next, participants completed a handgrip time-to-failure task by maximally squeezing an electronic handgrip dynamometer until they could no longer maintain 50% of their maximal voluntary contraction. Pairwise t-test revealed a non-significant difference between tDCS and SHAM conditions on handgrip time-to-failure $t(24) = 0.254$, $p = 0.401$. Separate 2 x 5 ANOVA's revealed no main effect of condition on changes in baseline HbO, HbR, and HbT for DLPFC and muscle hemodynamics (all $p > 0.05$). A linear mixed-effects model revealed no significant main effect of condition on recovery MVC ($p > 0.05$). This study provides evidence tDCS does not improve HGTTF in older adults, adding contrasting evidence regarding the effects of an acute session of tDCS. Further research is needed to confirm the ergogenic effects of acute tDCS.

Key Words: NEAR-INFRARED SPECTROSCOPY, AGING, MAXIMAL VOLUNTARY CONTRACTION, PERFORMANCE, FATUIGE

DEDICATION

This thesis is dedicated to my parents Hani and Roula Qadumi.

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This thesis follows the format prescribed by the American Psychological Association and the School of Health and Human Performance.

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CHAPTER ONE: INTRODUCTION

Currently, there are over 49 million Americans aged 65 years and older, making them the fastest-growing demographic in the United States (Beard et al., 2016; Indahlastari et al., 2021). As aging occurs, declines in the neuromuscular system can impact motor function and potentially restrict functional independence of older adults (Hunter et al., 2016; Prehn & Flöel, 2015). Individuals who experience reduced neural and motor system function face higher healthcare costs and a poorer quality of life (McGrath et al., 2019). Therefore, research efforts have been devoted to developing effective interventions to improve adults' motor function and independence as they age.

Transcranial direct current stimulation (tDCS) is one intervention strategy that is growing rapidly due to its practical applications in exercise rehabilitation and performance enhancement (Kan et al., 2013; Krishnan et al., 2014). Neuromodulation via tDCS is a non-invasive brain stimulation technique that emits a weak electrical current of ~1-2 mA through targeted brain regions (Hanson et al., 2021). Additionally, tDCS has been linked to improvements in the neuromuscular system by increasing the rate at which neurons fire as well as strengthening synaptic connections (Flöel, 2014; Lattari et al., 2016; Machado et al., 2019).

Several investigations have examined the acute effects of tDCS on the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) on aspects of muscular performance, such as muscular endurance (i.e., isometric time to failure (TTF)) (Alix-Fages et al., 2020; Cogiananian et al., 2007; Kan et al., 2013; Muthalib et al., 2013) and dynamic strength (i.e., maximal voluntary contraction (MVC)) (Lattari et al., 2016; Lattari et al., 2020). However, these studies utilized larger muscle groups such as the elbow flexors and knee extensors. Assessment of muscle function in larger muscle groups requires expensive equipment and may be impractical

for older adults (McGrath et al., 2021). Various measures of handgrip strength have been used to assess characteristics of muscle function and are non-fatiguing and inexpensive (McGrath et al., 2019). Because aging is associated with a decline in muscle function, the potential of tDCS to acutely improve muscle function in older adults may prove to be a useful tool in a variety of clinical settings. Thus, electronic handgrip dynamometry may be a more feasible assessment of tDCS on muscular performance in older adults.

To further understand the impact of tDCS on muscle function, it is essential to understand the neural mechanisms behind exercise performance and task termination. Research on tDCS has primarily targeted two brain regions: M1 and DLPFC, both regions are involved in exercise performance and task termination by driving the exercising muscle and processing internal and external cues related to exercise such as perceived effort respectively (Machado et al., 2019). Because M1 is not activated maximally at exercise termination it has been suggested the DLPFC may work as a compensatory mechanism to disregard interoceptive cues (i.e., vestibular senses), therefore reinforcing descending drive which may delay supraspinal fatigue (Robertson & Marino, 2016).

The effects of tDCS on DLPFC activity during exercise are not well understood. Near-infrared spectroscopy (NIRS) has commonly been used to assess DLPFC activity due to the accessibility of the DLPFC for NIRS application, and its role in exercise regulation (Auten et al., 2021). Prior investigations into NIRS have suggested neural activity induces changes in blood flow and when blood flow increases to activated brain areas, oxygen supply is greater than consumption (Herold et al., 2018). However, it is unclear whether tDCS induces changes in central and peripheral blood flow. Currently, to the best of our knowledge, there has been one study investigating the effects of tDCS prior to physical activity on muscle oxygenation, which

yielded no significant results (Auten et al., 2021). However, the aforementioned study utilized Halo Sport headphones (Halo Neuroscience, San Francisco, CA) to administer tDCS. Halo Sport headphones are a commercial device that do not factor in anatomical differences between participants and may influence other brain regions. Investigation into both brain and muscle oxygenation may provide important insights into the mechanism of action of tDCS during exercise.

To understand the mechanism of tDCS on motor function, it is essential to explore its effects on both fatigue and recovery. A consideration in this context is that sustained isometric muscular contractions impact physiological processes throughout the neuromuscular system, contributing to fatigue and prolonged recovery (Carroll et al., 2017). However, it is important to understand the effects of tDCS on motor recovery in healthy aging adults as this population requires a longer recovery period to return to baseline levels compared to their younger counterparts (Fell & Williams., 2008).

Therefore, the present study aims to investigate the effects of tDCS of the DLPFC in adults 60 years or older on: (1) Handgrip TTF task (HGTTF), (2) changes in muscle oxygenation of the DLPFC and peripheral muscle, and (3) MVC recovery. It is hypothesized that participants undergoing tDCS will show increased HGTTF as compared to the SHAM conditions, higher DLPFC activity as compared to the SHAM conditions, and increases in peripheral muscle oxygenation. Finally, we hypothesize that tDCS will accelerate post-test MVC recovery back to baseline.

CHAPTER TWO: Literature Review

Introduction

Neuromodulation through transcranial direct current stimulation (tDCS) is a brain stimulation technique that is non-invasive and easy to administer (Bikson et al., 2016; Jamil et al., 2017). The stimulation emits a weak electrical current of ~1-2 mA through a variety of different brain regions (Hanson et al., 2021). Placement of an anode electrode (a-tDCS) toward the nominal target is linked to increases in neuronal excitability and plasticity, following 10-30 minutes of stimulation (Lattari et al., 2018; Machado et al., 2019). The neuronal membrane potential controls the frequency of neuronal firing, by depolarizing the neuronal membrane tDCS increases the frequency of neuronal firing (Lefaucheur & Wendling, 2019). The placement of a cathode electrode (c-tDCS) near the nominal target is thought to have the opposite effect and is associated with suppressed neuronal excitability (Machado et al., 2019).

M1 and the DLPFC are two brain regions that play an essential role in the regulation and termination of exercise as a result these brain regions are commonly targeted for the application of tDCS (Hendy & Kidgell, 2013; Machado et al., 2019). M1, located in the precentral gyrus of the frontal lobe, is crucial for exercise performance due to its role in driving the exercising muscle (Bhattacharjee et al., 2021; Machado et al., 2019). Betz cells, also known as upper motor neurons, are mainly located in M1 and send axons to lower motor neurons in the grey column of the spinal cord. Whereas the lower motor neurons innervate skeletal muscle fibers at the periphery. During exercise, the excitability of spinal motor neurons decreases. To maintain the desired intensity for exercise, input to these spinal motor neurons must increase. This input is termed descending drive, and failure of M1 to maintain descending drive, termed supraspinal fatigue contributes to the onset of exercise termination (Angius et al., 2017; Bhattacharjee et al.,

2021; Machado et al., 2019). Therefore, one reason for using tDCS over M1 would be to increase neuronal excitability of the motor neurons in M1, which would delay supraspinal fatigue, therefore delaying exercise termination. However, motor control function of the brain is closely tied to its sensory function as both functions rely on information transmission from the brain to the spinal cord, as well as from the peripheral receptors to the brain. The DLPFC, located in the middle frontal gyrus, comprises multiple components within the prefrontal cortex. It is connected to many other brain regions through an extensive network, resulting in a robust structural and functional system for processing sensory information and decision making in the brain (Anguis et al., 2017; Bigliassi, 2022; Machado et al. 2019; Robertson & Marino, 2016).

Previous investigations have indicated the DLPFC acts as a compensatory mechanism for M1, as the DLPFC may disregard interoceptive cues (i.e., vestibular senses) which may prolong the motor drive and postpone the onset of supraspinal fatigue, as a result, exercise termination may be delayed (Anguis et al., 2017; Machado et al., 2019; Robertson & Marino, 2016). Therefore, tDCS of the DLPFC may allow this brain region to disregard sensory information related to exercise for a longer period of time by increasing neuronal activity. However, tDCS mechanism of action is not fully understood. Liebetanz (2002) suggests voltage-dependent N- methyl-D-aspartate receptors mediate synaptic strength by potentially providing an increase in intracellular Ca^{2+}, in both animals and humans. When given dextromethorphan, an N-methyl- D-aspartate – receptor blocker, neuroplastic changes in M1 were prevented (Liebetanz, 2002). Additionally, previous neuroimaging studies have demonstrated decreased DLPFC oxygenation before the onset of fatigue (Machado et al., 2019; Thomas & Stephane, 2008). Suggesting a-tDCS over M1 or DLPFC may increase neuronal excitability by increasing intracellular Ca^{2+}, exercise tolerance, and improving

muscular fitness.

Therefore, the scope of this literature review is to investigate the effects of tDCS of M1 and the DLPFC on muscular fitness in resistance training exercise sessions. Furthermore, this review looks to explore the effects of a-tDCS on MVC, movement velocity, repetitions to failure (RTF), TTF, and perceived effort.

Muscle Endurance

Training volume (e.g., number of repetitions) plays a crucial role in the adaptations induced by resistance training, as high training volumes are correlated with greater adaptations in muscular hypertrophy and strength (Alix-Fages et al., 2020). Additionally, isometric exercises have been incorporated into athletes' training, as these exercises may promote positive neuromuscular adaptations to improve strength (Lum & Barbosa, 2019). Therefore, it is important to investigate the effects of a-tDCS on RTF as well as isometric endurance assessed via TTF tasks.

Repetitions to Failure

Studies investigating the effects of a-tDCS over the DLPFC on volume load and RTF have consistently shown a positive effect (Alix-Fages et al., 2020; Lattari et al., 2016; Lattari et al., 2020). Alix-Fages and colleauges (2020) investigated the effects of a-tDCS on volume load (i.e., total number of repetitions) with the bench press exercise in healthy men (n = 14; age = 22.8 ± 3.0 years) and found an increase in total repetitions performed during a resistance training session following a-tDCS. Lattari and colleagues (2016) sought to determine the effects of a-tDCS on volume load with a maximum load free barbell elbow flexion exercise in undergraduate students (n = 10; age = 26.5 ± 5.0 years) and found after participants underwent the a-tDCS

condition, volume load was higher as compared to c-tDCS and SHAM conditions. Lattari and colleagues (2020) conducted a similar study investigating a-tDCS on volume load with the leg press exercise in young healthy adults (n = 15; age = 24.5 ± 3.3 years) and found an increase in volume load following a-tDCS.

In summary, a-tDCS delivered over the DLPFC results in significant increases in volume load (Alix-Fages et al., 2020; Lattari et al., 2016; Lattari et al., 2020). This may be due to the vast functional system of the DLPFC. The DLPFC is not directly connected with major motor control regions, however, it is indirectly linked via the premotor area (Robertson & Marino, 2016). The premotor area and regions of the prefrontal cortex, such as the lateral prefrontal cortex and orbitofrontal prefrontal cortex, are areas of the brain that have a role in cognitive and emotional function (i.e., motivation, reward, planning, and execution) that are involved in the ability to increase exercise tolerance (Robertson & Marino, 2016). Additionally, the neuronal membrane potential controls the frequency of neuronal firing. By altering the neuronal membrane potential (i.e., depolarizing the neuron) tDCS increases the frequency of neuronal firing (Prehn & Flöel, 2015). Increasing the neuronal firing rate may prolong DLPFC activation, allowing individuals to exercise for a longer period of time. However, these studies failed to include measurements of DLPFC activation.

These findings are not without limitations, the aforementioned studies had a limited subject pool focused on healthy, resistance-trained males (Alix-Fages et al., 2020; Lattari et al., 2016; Lattari et al., 2020). Thus, studies should look to incorporate women as changes in cortical excitability and large variability in muscle function may exist between genders (Lattari et al., 2016). Lastly, there are a limited number of studies investigating the effects of tDCS on motor performance in healthy older adults (Fujiyama et al., 2014; Hummel et al., 2010; Zimerman et

al., 2013). As previous research has observed a delayed plastic response in healthy older adults compared to younger adults following 30-minutes of a- tDCS over M1, future investigations into tDCS on motor performance should involve healthy older adults of both genders (Fujiyama et al., 2014).

Time to Failure

Fatigue is experienced both physically and cognitively. The physical experience involves task performance over time, while the cognitive includes perceived effort. By controlling the motor drive, which is essential for the activation of motor units, M1 is a key regulator of endurance tasks (Alix-Fages et al., 2019). It has been suggested tDCS may delay supraspinal fatigue by increasing the output of M1 (Alix-Fages et al., 2019; Williams et al., 2013). However, researchers investigating the effects of a-tDCS over M1 on TTF have showed mixed results (Cogiananian et al., 2007; Kan et al., 2013; Muthalib et al., 2013). Cogiananian and colleagues (2007) investigated the effects of a-tDCS on isometric endurance time (TTF task) of the left elbow flexors in healthy, right-handed individuals (n = 24, 14 women and 10 men; age = 24.3 years. The results of this study showed a significant effect ($p < 0.05$) on endurance time in the a-tDCS condition. Similarly, Kan and colleagues (2013) sought to investigate the effects of a-tDCS over the right M1 on the left elbow flexor during a TTF task in healthy men (n = 15; age = 27.7 ± 8.4 years). The results of this study showed no significant changes in TTF between interventions ($p > 0.05$). A separate study looked to examine the effects of a-tDCS of the motor cortex on PFC- oxygenation during a sustained submaximal isometric contraction of the elbow flexors until task failure (i.e., TTF) in healthy men (n = 15; age = 27.7 ± 8.4 years) (Muthalib et al., 2013). The results of this study showed no significant differences ($p > 0.05$) between a- tDCS and SHAM conditions on elbow flexor TTF.

The results from researchers investigating a-tDCS and its effects on TTF indicate a-tDCS has no effect on TTF (Cogiananian et al., 2007; Kan et al., 2013; Muthalib et al., 2013). Nonetheless these findings have certain limitations. The DLPFC has an important role in exercise regulation and influences exercise termination by processing internal and external cues related to exercise such as knowledge of exercise endpoint and distance/time remaining (Machado et al., 2019). Therefore, the DLPFC may have been a more appropriate brain region to stimulate rather than M1 for muscular endurance exercise activities. These studies are the first to assess isometric TTF following a-tDCS over M1, specifically in small muscle groups (i.e., elbow flexors). The main objective of these studies was to assess muscle function in terms of neuromuscular fatigue, defined as the exercise- dependent decrease in muscle force (Cogiamanian et al., 2007). However, assessing TTF by completing multiple fatiguing tasks in one laboratory session is impractical in older populations as these subjects may be more easily fatigued than younger adults (Allman & Rice et al., 2002). As a result, the investigation into the effects of tDCS on muscular endurance assessed via TTF, excluding a baseline fatiguing task is warranted in both younger and older healthy adults.

Muscular Strength and Power

Muscular strength plays an important role in athletic performance and is directly associated with physical performance, sport technique, injury prevention, and rehabilitation of injuries (Vargas et al., 2018). Previous studies have consistently shown an increase in 1-RM, and observed contrasting results on the effects of a-tDCS over M1 on MVC with some studies indicating no effect while others observed a positive effect (Hazime et al., 2017; Kamali et al., 2019; Lu et al., 2021). Hazime and colleauges (2017) investigated whether tDCS increased the isometric muscle strength of shoulder external and internal rotators in female handball athletes

(*n* = 8; age = 19.7 ± 2.3 years), and found a significant increase in maximal voluntary isometric contraction of the internal and external rotators across multiple time points when participants underwent a-tDCS of M1. Kamali and colleagues (2019) sought to determine the effects of a-tDCS over M1 and the temporal cortex on 1-RM of the knee extensors in experienced bodybuilders (*n* = 12; age = 25.6 ± 6.0 years). Results from Kamali and colleauges (2019) indicate that a-tDCS increased 1-RM by 4.4% as compared to SHAM conditions. Lu and colleagues (2021) stimulated M1 in an attempt to increase knee muscle strength in healthy adult males (*n* = 19; age = 23.3 ± 2.4 years) and found knee flexor and extensor force output increased immediately after and 30 minutes following a-tDCS.

Results from the previously mentioned studies indicate a-tDCS over the M1 may lead to an increase in maximal voluntary isometric contraction and 1-RM. This could be due to increased neuronal excitability of M1, delaying the onset of supraspinal fatigue and prolonging contraction strength.

Movement Velocity

A loss of velocity is indicative of neuromuscular fatigue, as a result velocity-based training has gained popularity as a way of monitoring fatigue (Guerriero et al., 2018). Neuromodulation through tDCS aims to increase neuronal excitability of key motor and sensory control regions of the brain, which may delay the onset of neuromuscular fatigue. Therefore, it is important to discuss the potential effects of tDCS on movement velocity during a training session.

Previous investigations into the effects of tDCS on movement velocity have primarily targeted the DLPFC and have consistently shown insignificant results (Alix-Fages et al., 2020;

Garcia-Sillero et al., 2022; Rodrigues et al., 2022). Rodrigues and colleagues (2022) investigated the effects of a-tDCS over the DLPFC on movement velocity in healthy men (*n* = 12; age = 24.8 ± 3.0) during the bench press exercise and found no significant difference between a-tDCS, c-tDCS and SHAM conditions. Garcia-Sillero and colleagues (2022) investigated the effects of a-tDCS over the DLPFC on movement velocity during the back-squat exercise in male firefighters (*n* = 16; age = 34.7 ± 3.3 years). The results of this study showed no significant differences in movement velocity between the a-tDCS and SHAM interventions.

Alix-Fages and colleagues (2020) examined the effects of a-tDCS applied over the DLPFC on movement velocity in healthy men (n = 14; age = 22.8 ± 3.0 years) during the bench press exercise. The study found no significant main effect of condition (a-tDCS, c-tDCS, and SHAM) on movement velocity. However, a significant interaction between condition and set was observed, with participants showing smaller decrements in movement velocity between sets under a-tDCS conditions. Additionally, the study revealed a notable increase in the number of repetitions in the a-tDCS condition compared to c-tDCS and SHAM.Suggesting a-tDCS may be effective in mitigating velocity loss throughout a training session. This is important in terms of muscle performance as previous research has suggested once a given velocity loss is reached the resistance training session should be terminated (Alix-Fages et al., 2020; Pareja-Blanco et al., 2017).

Based on the aforementioned studies, a-tDCS over the DLPFC does not influence mean movement velocity throughout a training session. Findings from Alix-Fages and colleagues provide novel insight into the effects of tDCS on movement velocity. Suggesting that tDCS may help to mitigate velocity loss between sets, theoretically mitigating

neuromuscular fatigue.

Perceived Exertion

Increasing neuronal excitability via a-tDCS may promote positive effects in the DLPFC, a region of the brain that regulates perceived effort during exercise (Fortes et al., 2021; Machado et al., 2019). This may decrease perceived effort when training at similar intensities (Lattari et al., 2020). Previous research has investigated the effects of tDCS over both the DLPFC and M1 on rating of perceived exertion (RPE) and has shown mixed results, with some studies observing a positive effect (Alix-fages et al., 2020; Fortes et al., 2021; Lattari et al., 2016) and other studies showing no effect (Lattari et al., 2018). These discrepancies may be attributed to the different RPE scales used between studies. The OMNI perceived exertion scale for resistance training (OMNI-RES), is a scale that has verbal and mode-specific pictures that correspond to a numeric response on a 0 to 10 scale (Lattari et al., 2018). Fortes et al., (2021) sought to understand the effects of a- tDCS on session RPE 30 minutes after the resistance training exercise session, stating that traditional RPE may fail to indicate actual effort performed by the subject. To the best of my knowledge, this is the only study assessing tDCS on RPE, and further investigation is warranted on the reproducibility of these effects.

Gaps in Literature

Despite being regarded as an ergogenic aid, several gaps remain in the literature regarding tDCS and its effects on muscular performance. Firstly, studies examining TTF tasks have targeted M1 for stimulation. However, the DLPFC may be a more appropriate region for such interventions due to its role in sensory processing and its top-down influence on M1. Secondly, the majority of researchers investigating the use of tDCS as an ergogenic aid have utilized young healthy adults, mainly males. Results from these studies may not be transferable

to older populations who tend to have more compromised neuromuscular systems as previously discussed. Lastly, researchers stimulating the DLPFC have focused on dynamic, large muscle group exercises such as cycling, bench and leg press exercises. These movement patterns may be impractical for older adults. Handgrip testing has been used to assess characteristics of muscle function and are non-fatiguing making electronic handgrip dynamometry a feasible assessment of tDCS on muscular performance in older adults.

Summary of Literature

In summary, a-tDCS over the DLPFC seems to improve muscular endurance when assessing volume load and RTF (Alix-fages et al., 2020; Lattari et al., 2016; Lattari et al., 2020). There were inconsistent results in studies measuring the effect of a-tDCS on TTF tasks, muscular strength, and RPE. Studies investigating movement velocity following a-tDCS regularly found no effect. However, a-tDCS over the DLPFC may improve velocity loss in a sets-to-failure design method.

CHAPTER 3: METHODS

Participants

25 healthy adults aged 60 years or older volunteered to participate in this study (descriptive statistics reported in Table 1). Participants were excluded from this study if they had a history of stroke or heart attack, were admitted for transient ischemic episodes or angina within the past six months, had any serious conditions like cancer, were unable to comply with study demands, had a history of or currently had a neurological or psychiatric disorder, had a musculoskeletal injury or disorder that prevented gripping tasks such as arthritis, were not ready to participate in physical activity as determined by the PAR-Q+, or had a metallic implant in the brain (Keel et al., 2000). All participants completed the tDCS Safety Screening Questionnaire to validate their eligibility for participation in this study (Keel et al., 2000). In addition, participants were required to complete the Edinburgh Handedness test to determine handedness (Oldfield, 1971). Sample size calculations for a randomized, single-blinded, SHAM-controlled, cross-over design were used to detect a change in HGTTF between tDCS conditions. An effect size of d=0.29 was calculated using descriptive statistics from Anguis and colleagues (2019), with a power level of 0.8 and an alpha level set at .05, producing a total sample size of 30 participants. Following the initial screening, the participants were given informed consent which conveyed both the study objectives and associated risks involved. This study was approved by the Northern Michigan University Institutional Review Board, approval number: HS23-1371.

Table 1: Participant Descriptive Statistics (n = 25).

Variable	Mean ± SD
Age (years)	71.08 ± 5.64
Body mass (kg)	75.87 ± 16.45
Gender (%, male)	40%
Handedness (%, right)	95%

Procedures

In this randomized, single-blinded, SHAM-controlled, cross-over design, participants completed a HGTTF task after undergoing tDCS or SHAM control conditions. Participants were asked to avoid strenuous physical activities for 48 hours prior to their visit and maintain habitual sleeping, eating, and hydration patterns. Subjects attended two laboratory sessions, tDCS or SHAM (described below) in a random order lasting one hour each, separate by 48 hours. 10 minutes after the stimulation, participants completed a HGTTF task. Following task termination, participants preformed 5s MVCs immediately, 1-, 5-, and 10-minutes after task termination. Post-test MVCs were recorded and used to measure reductions in neuromuscular strength and subsequent recovery. NIRS was used to examine DLPFC and muscular hemodynamics during the TTF task.

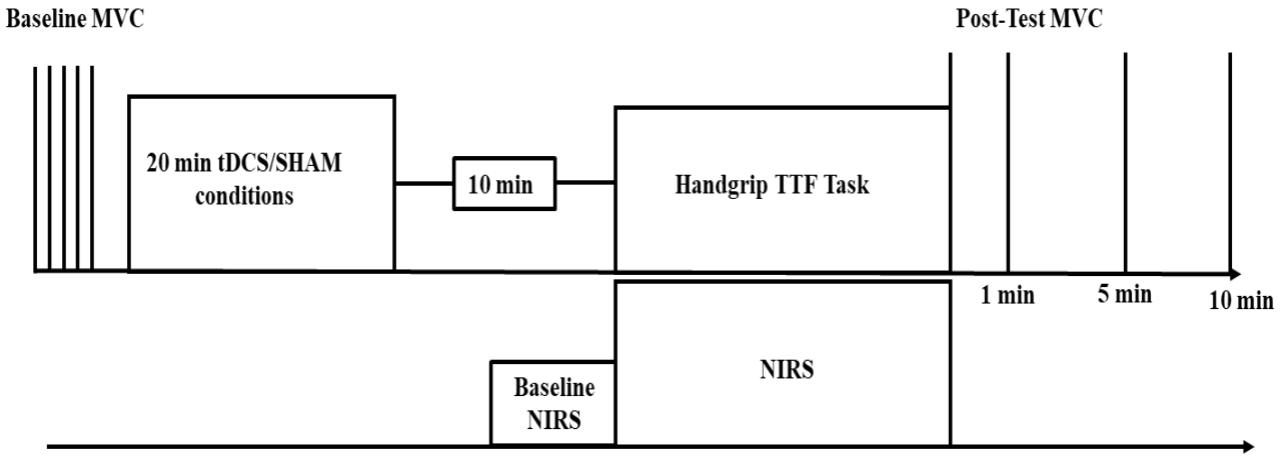

Figure 1: Experimental Overview. MVC = Maximal Voluntary Contraction, tDCS = Transcranial Direct Current Stimulation, TTF = Time-to-Failure, NIRS = Near-Infrared Spectroscopy.

Application of Transcranial Direct Current Stimulation

Prior to the HGTTF, participants were seated comfortably in a chair with their arm rested at approximately 90 degrees and underwent one of two conditions. For both tDCS and SHAM conditions, the anode electrode was placed over the left dorsolateral prefrontal cortex located in the electrode area F3 according to the tDCS 10/20 Electrode Placement Cap (Caputron, New York, USA). The cathode electrode was placed over the right orbitofrontal cortex located in the electrode area Fp2, this protocol is consistent with that of Lattari and colleagues (2016). In the tDCS condition, an electric current of 2.0 mA was applied for 20 minutes using a pair of 3x3-inch pads soaked in a saline solution (0.9% NaCl), connected to an ActivaDose tDCS (Caputron, New York, USA) and positioned using the tDCS 10/20 electrode Placement Cap. For the SHAM condition, electrical stimulation of 2.0 mA was delivered for 30s and ramped down to 0 mA without informing the participant, subjects remained seated for 20 minutes. By turning off the stimulation after 30s participants received the sensations of stimulation without the aftereffects

associated with tDCS such as increased neuronal firing; this protocol is consistent with that of Lattari and colleagues (2016).

Handgrip Procedures

Participants performed baseline MVCs using a Biopac electronic handgrip dynamometer (Biopac Systems, Goleta, CA). Participants were instructed to squeeze the electronic dynamometer at their absolute maximum effort for ~5s, participants repeated this for a total of five MVCs with 60s rest in between each set. Participants were instructed to "squeeze as hard as possible" and standardized verbal encouragement was provided to the participants by the investigators. The average of the two highest values were used as baseline MVC, data was processed at a sampling rate of 10 Hz (Mahoney et al., 2020). After both tDCS and SHAM conditions and application of the NIRS system, subjects remained seated with their elbow flexed at 90 degrees, and their forearm in a neutral position. Following a 30-minute resting period (20 minutes of stimulation followed by 10-minute rest), subjects were instructed to squeeze the handgrip dynamometer as hard as possible until they could no longer maintain 50% of the baseline handgrip strength for 3s. Subjects were also instructed not to pace themselves and were verbally informed once they could no longer maintain 50% MVC. The duration of this contraction was recorded as TTF in seconds.

Following task termination, subjects performed MVCs on the handgrip dynamometer immediately after, 1-, 5-, and 10-minutes post-test. Instantly after the task termination subjects were prompted by the investigator to release their grip from the dynamometer for ~1s and immediately perform a handgrip dynamometer MVC. Grip force was collected throughout the protocol. The peak force value in kilograms for each post-test MVC was recorded.

Central Oxygenation

Throughout the HGTTF task, DLPFC hemodynamics were measured by observing the changes from baseline in oxygenated (HbO), deoxygenated hemoglobin (HbR), and total hemoglobin (HbT) via NIRS. Data was recorded at a sampling rate of 50 Hz. the NIRS headband was centered with the nasion and secured to the participant's forehead, just above the supraorbital ridge (Phillips et al., 2020). The headband was secured with elastics and all lighting (i.e., overhead and monitor lighting) in the laboratory was dimmed to prevent contamination of the NIRS signal. Participants were asked to relax for approximately two-minutes, and a 30s baseline measurement was performed. During this time, participants were instructed to sit still with their eyes open, breathe normally, and not control their mental activity in any particular way. Additionally, participants were asked to minimize head and body movements throughout the experiment to reduce artifacts in the signal (Phillips et al., 2020). During the HGTFF, a 3s average of HbO, HbT, and HbT at 0%, 25%, 50%, 75%, and 100% TTF was collected for data analysis. Data was collected using the TechEn CW6 (MA, USA) with 9 probes (16 channels) placed on the forehead of the participant. The TechEn CW6 employs 690 nm and 830 nm wavelengths to calculate concentration changes in HbO and HbR. Data was used to analyzed using Homer3 (Boston University, USA) which is an open-source MATLAB (MathWorks, Inc. USA) application used for analyzing NIRS data to acquire estimates of brain activation (Huppert et al., 2009).

Muscular Oxygenation

Muscle oxygenation levels during the HGTTF task were measured from the flexor carpi radialis (FCR) using a continuous-wave NIRS device (PortaLite; Artinis Medical Systems BV, Elst, Netherlands). Sensors were placed on the FCR of the right forearm approximately 1/3 of the distance from the medial epicondyle of the humerus to the styloid process of the radius, this protocol is consistent with that of Kilgas and colleagues (2019). NIRS was utilized to detect changes in baseline concentrations of HbO, HbR, and HbT. Wavelengths (760 and 850 nm) were emitted from LEDs with an inter-optobe distance of 3.5 cm. A differential path-length factor of 4.0 was used to correct for photon scattering within the tissue (Kilgas et al., 2022). The sensor was attached with double-sided tape and wrapped in an opaque bandage to prevent ambient light from reaching the sensor. Data was recorded at a sampling rate of 10 Hz and a 30 second resting baseline was recorded, a 3s average of HbO, HbT, and HbT at 0%, 25%, 50%, 75%, and 100% TTF was collected for data analysis. NIRS has been shown to be a reliable tool for measuring low-force repetitive tasks in contracting muscles (Celie et al., 2012; Matooth et al., 2018; Murthy et al., 1997).

Statistical Analysis

In this cross-over design, a paired-samples t-test was used to analyze the effect of the condition (tDCS and SHAM) on TTF. Additionally, six separate 2 × 5 repeated measures ANOVAs were used to analyze the effect of condition (tDCS and SHAM) and time (0%, 25%, 50%, 75%, and 100% TTF) and the interaction between condition and time on DLPFC and muscle oxygenation. Statistical procedures were performed using IBM SPSS 24 (Chicago, IL,

USA) an alpha of 0.05 was used to detect statistical significance, and data is reported as mean ± SD.

Additionally, the lme4 package (version 1.1-35.1) in Rstudio (version 2023.12.1+402, Posit Software) was used to investigate the effects of condition and time on recovery MVC, a linear mixed effects model was fit by REML using Satterthwaite's method for main effects. The Kenward-Roger approximation for degrees of freedom and Bonferroni method were utilized for pairwise comparisons. The model included fixed effects for condition (tDCS vs SHAM), time (baseline, immediately after, 1-, 5-, and 10-minutes post TTF), and the interaction of condition and time. Random intercepts for subjects were included to account for repeated measures within subject's design. The model specification was as follows: m <- lmer(MVC ~ Time * Group + (1|Participant_ID).

Effect size analysis was conducted to report the magnitude of differences between conditions for HGTTF and both muscle oxygenation of the DLPFC and peripheral muscle oxygenation. Cohens D effect sizes were classified as trivial ($d < 0.19$), small ($d = 0.20–0.49$), moderate ($d = 0.50–0.79$), large ($d = 0.80–1.29$), and very large (>1.30) (Lattari et al., 2020). *ηp2* effect sizes were classified as small (ηp^2 =0.01), medium (0.06), and large (0.14) (Valenzuela-Rios et al., 2024).

CHAPTER FOUR: RESULTS

Handgrip Time-to-Failure

Pairwise t-test revealed a non-significant difference between tDCS and SHAM conditions $t(24) = 0.254$, $p = 0.401$ and represented a trivial-sized effect $d = 0.05$ (Figure 2).

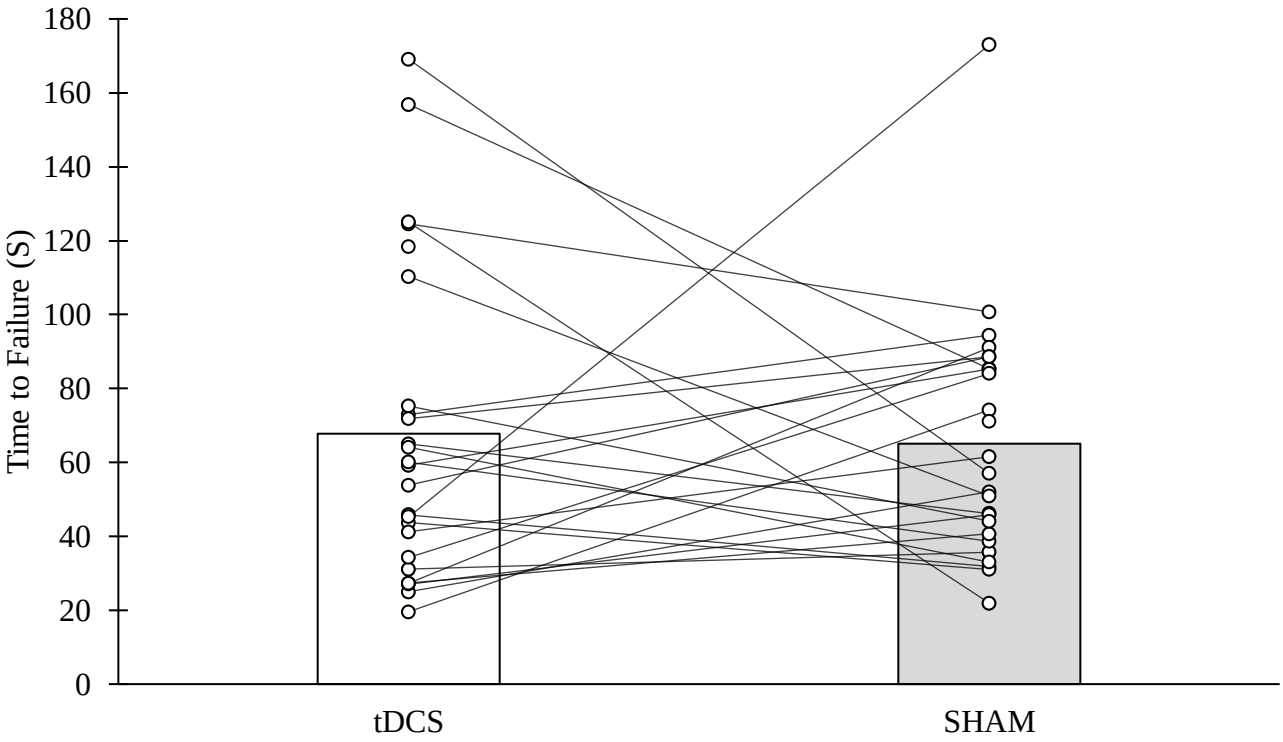

Figure 2: Effect of tDCS on handgrip TTF. tDCS = transcranial direct current stimulation.

Central Near-Infrared Spectroscopy

A 2 × 5 repeated measures ANOVA revealed no significant interaction of condition × time on changes in baseline HbO $F(1.877, 45.045) = 0.792$, $p = 0.452$, $\eta p2 = 0.032$. There was no main effect of condition on changes in baseline HbO $F(1, 24) = 0.523$, $p = 0.476$, $\eta p2 = 0.21$ (Figure. 3). There was a significant main effect of time on changes in HbO values $F(1.212,$

29.097) = 23.338, $p < 0.001$, $\eta p2 = 0.493$. Pairwise comparisons using the Bonferroni correction revealed significant differences across all time point (all $p < 0.05$) except between 50% and 100% TTF ($p > 0.05$), and 75% and 100% TTF ($p > 0.05$).

A separate 2 × 5 repeated measures ANOVA revealed no significant interaction between condition × time on changes in baseline HbR $F(2.633, 63.198) = 0.321$, $p = 0.784$, $\eta p2 = 0.13$. There was no main effect of condition on changes in mean baseline HbR $F(1,24) = 0.133$, $p = 0.718$, $\eta p2 = 0.006$ (Figure. 4). There was a significant main effect of time on changes in baseline HbR $F(2.256, 54.153) = 32.424$, $p < 0.001$, $\eta p2 = 0.575$. Pairwise comparisons using the Bonferroni correction revealed significant differences between 0% and 50, 75 and 100% ($p < 0.05$), however no significant differences were observed between 50%, 75% and 100% TTF.

A separate 2 ×5 repeated measures ANOVA revealed no significant interaction between condition × time on change in baseline HbT $F(1.893, 45.436) = 0.473$, $p = 0.616$, $\eta p2 = 0.019$. There was no main effect of condition on changes in baseline HbT $F(1,24) = 0.620$, $p = 0.439$, $\eta p2 = 0.025$ (Figure 5). There was a main effect of time on changes in baseline HbT $F(1.193, 28.633) = 10.518$, $p = 0.002$, $\eta p2 = 0.305$. Pairwise comparisons using the Bonferroni correction revealed no significant differences between 0% and 100% TTF in mean HbT changes from baseline ($p > 0.05$).

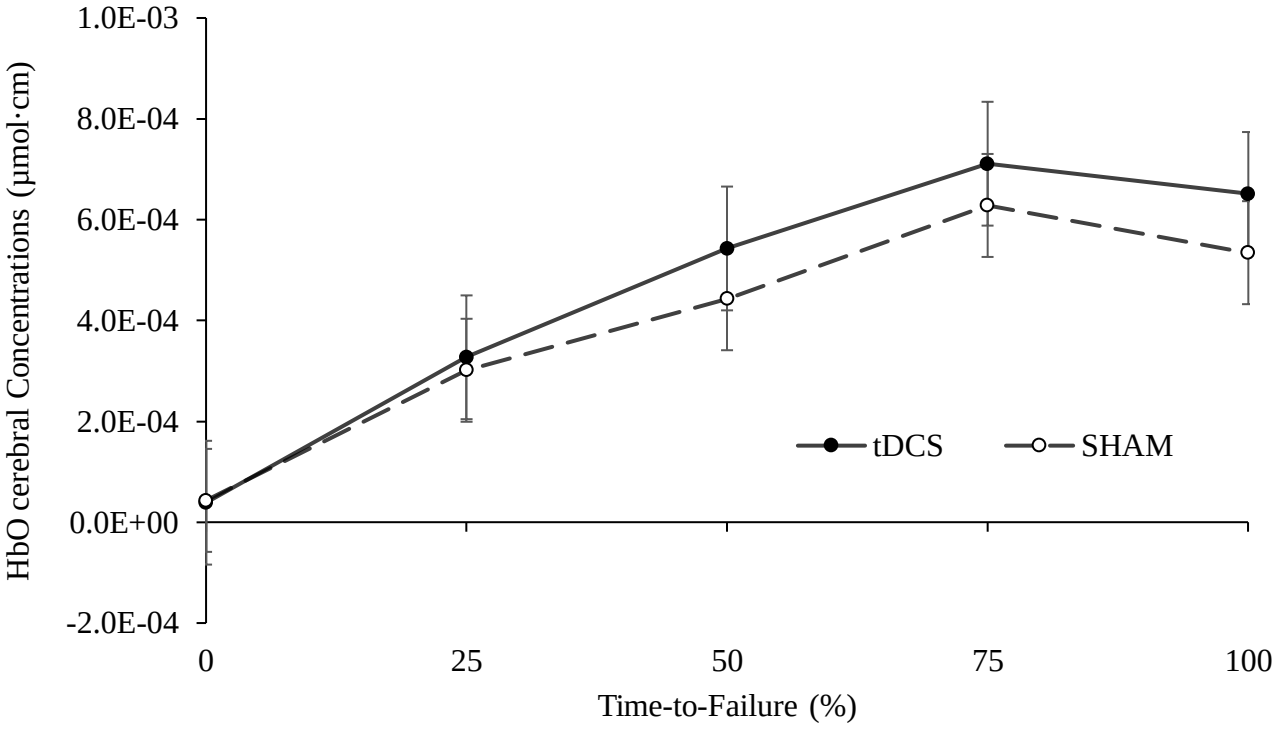

Figure 3: Oxygenated hemoglobin central concentration changes from baseline measured during handgrip time-to-failure. HbO = oxygenated hemoglobin. Data are reported as mean ± SE. Oxygenated hemoglobin different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

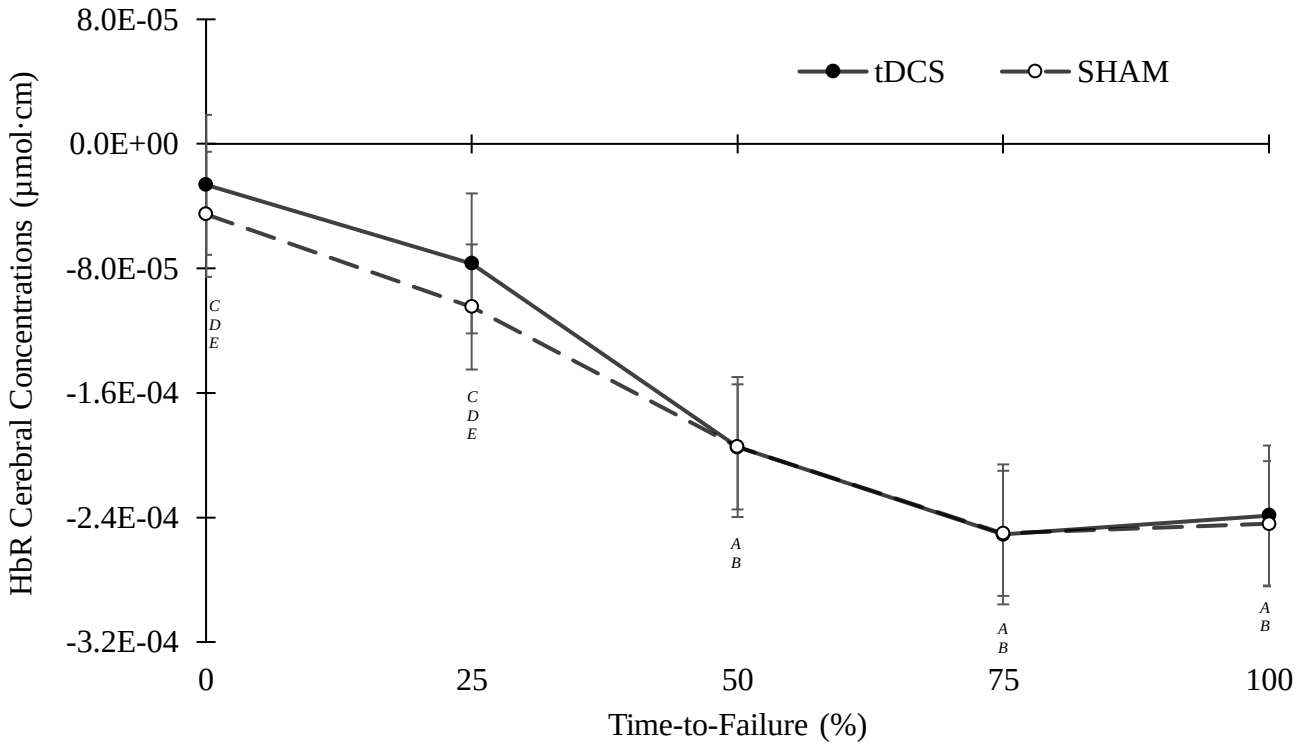

Figure 4: Deoxygenated hemoglobin central concentration changes from baseline measured during handgrip time-to-failure. HbR = deoxygenated hemoglobin. Data are reported as mean ± SE. *$p < 0.05$ indicates a significant main effect for time. Deoxygenated hemoglobin different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

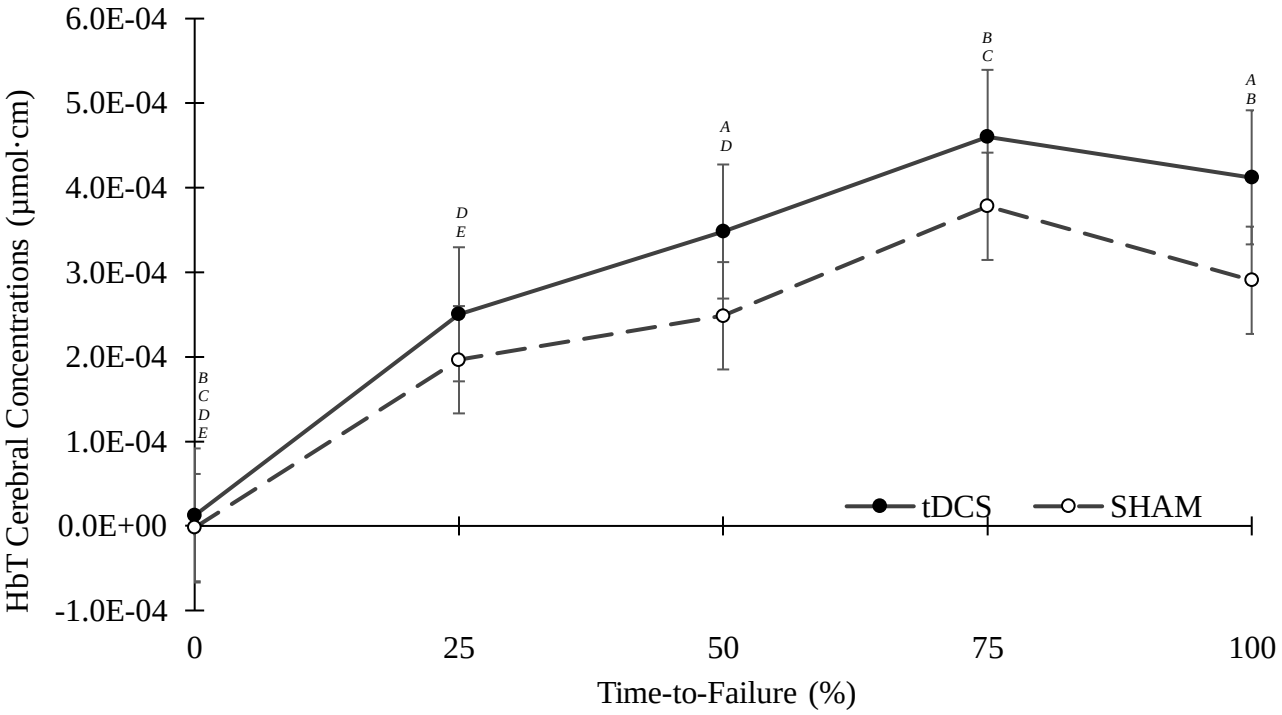

Figure 5: Total hemoglobin (oxygenated – deoxygenated hemoglobin) central concentration changes from baseline measured during handgrip time-to-failure. HbT = total hemoglobin. Data are reported as mean ± SE. *$p < 0.05$ indicates a significant main effect for time. Total hemoglobin different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

Muscular Near-Infrared Spectroscopy

The 2 ×5 repeated measures ANOVA revealed no significant interaction of condition x time on changes in baseline HbO, $F(2.176, 34.809) = 1.164$, $p = 0.327$, $\eta p2 = 0.068$. There was no significant effect of condition on changes in baseline HbO, $F(1, 16) = 0.49$, $p = 0.827$, $\eta p2 = 0.003$ (Figure 6). However, there was a significant effect of time on changes in baseline HbO, $F(1.291, 20.660) = 5.811$, $p = 0.019$, $\eta p2 = 0.266$. Despite the significant effect of time, pairwise comparisons using the Bonferroni correction revealed no significant differences across all time points (all $p > 0.05$).

A separate 2 × 5 repeated measures ANOVA revealed no significant interaction of condition × time on changes in baseline HbR $F(2.376,38.020) = 0.995$, $p = 0.391$, $\eta p2 = 0.120$. there was no significant effect of condition on changes in baseline HbR $F(1,16) = 0.035$, $p = 0.854$, $\eta p2 = 0.002$ (Figure 7). However, there was a significant main effect of time on HbR $F(1.749,27.988) = 19.266$, $\eta p2 = 0.546$. Pairwise comparisons using the Bonferroni correction revealed significant differences across all time points (all $p <0.05$), except for 0% and 25% TTF ($p > 0.05$).

A separate 2 × 5 repeated measure ANOVA revealed no significant interaction between condition and time $F(2.532,40.511) = 0.381$, $p = 0.734$, $\eta p2 = 0.23$. HbT values were not significantly affected by condition $F(1,16) = 0.063$, $p = 0.805$, $\eta p2 = 0.004$ (Figure 8). However, there was a significant interaction of time on changes in baseline HbT $F(1.667,26.665) = 6.005$, $p = 0.010$, $\eta p2 = 0.273$. pairwise comparisons using the Bonferroni correction revealed significant differences between 0% and 100% TTF, and differences between 25%, 75%, and 100% TTF (all $p < 0.05$).

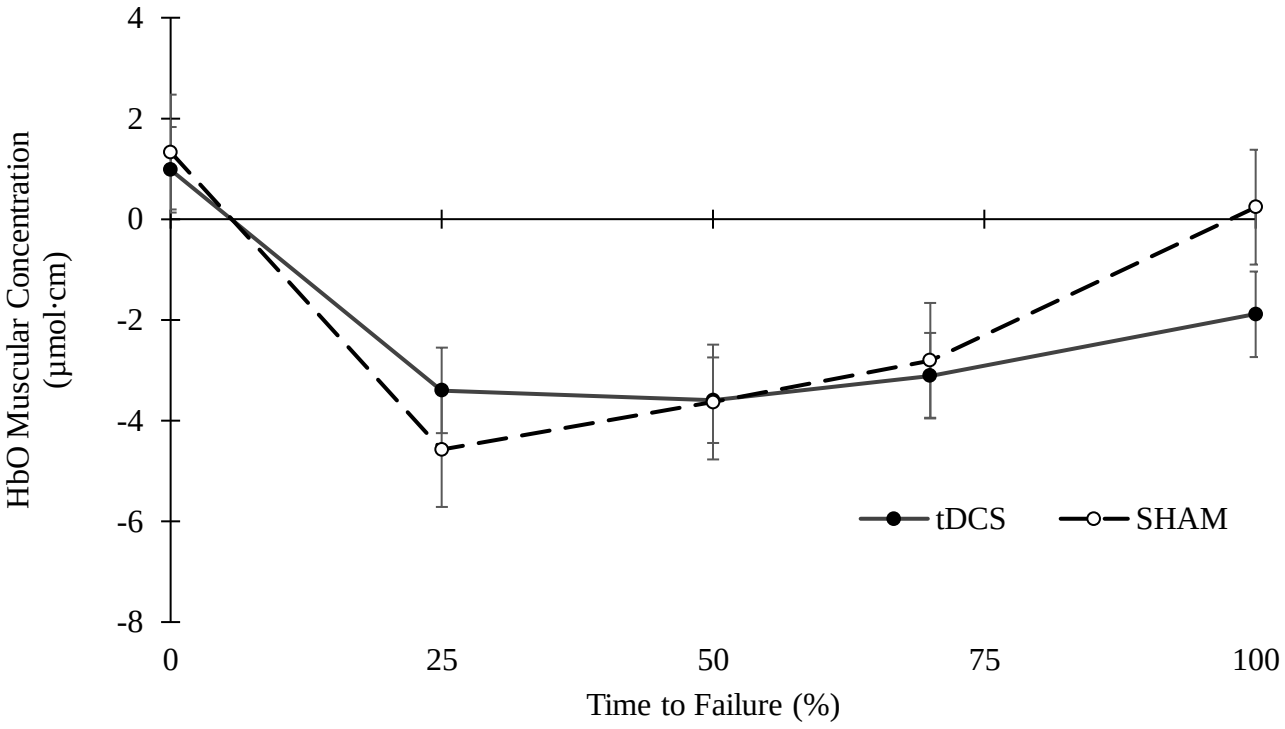

Figure 6: Oxygenated hemoglobin muscular concentration changes from baseline measured during handgrip time-to-failure. HbO = oxygenated hemoglobin. Data are reported as mean ± SE. *$p < 0.05$ indicates a significant main effect for time. Oxygenated hemoglobin different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

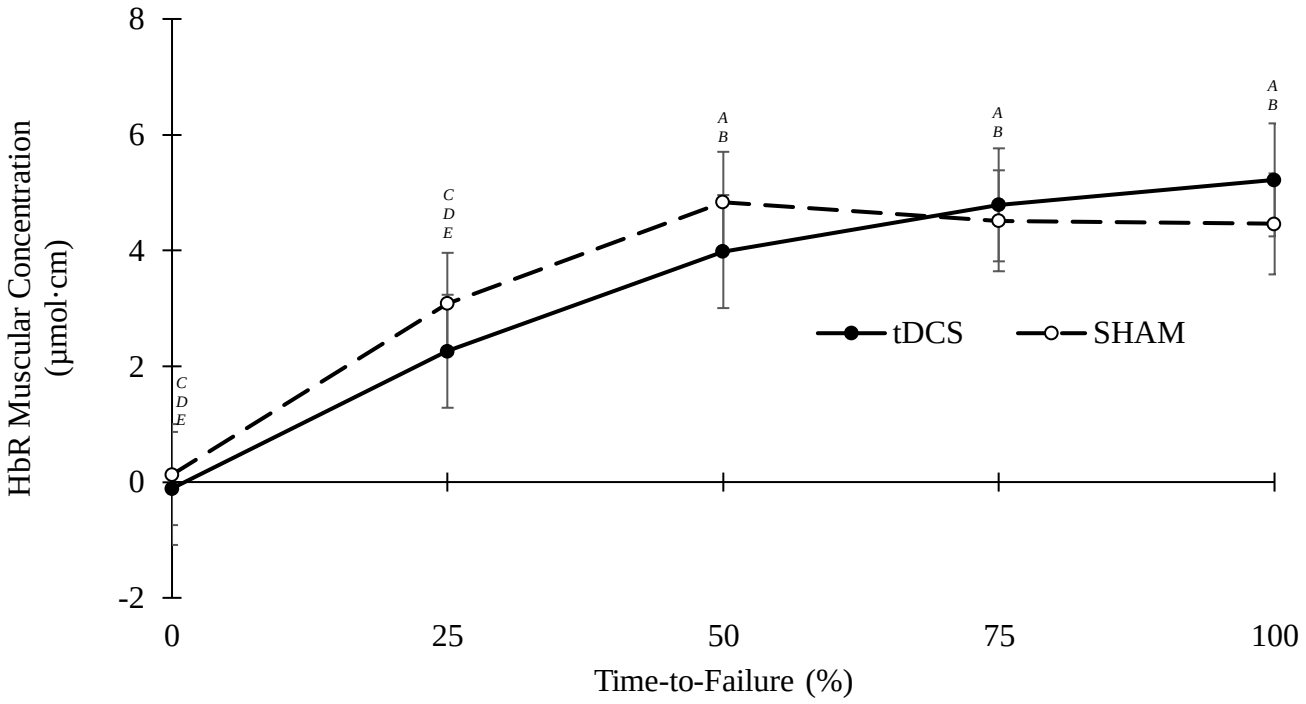

Figure 7: Deoxygenated hemoglobin muscular concentration changes from baseline measured during handgrip time-to-failure. HbR = deoxygenated hemoglobin. Data are reported as mean ± SE. *$p < 0.05$ indicates a significant main effect for time. Deoxygenated hemoglobin different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

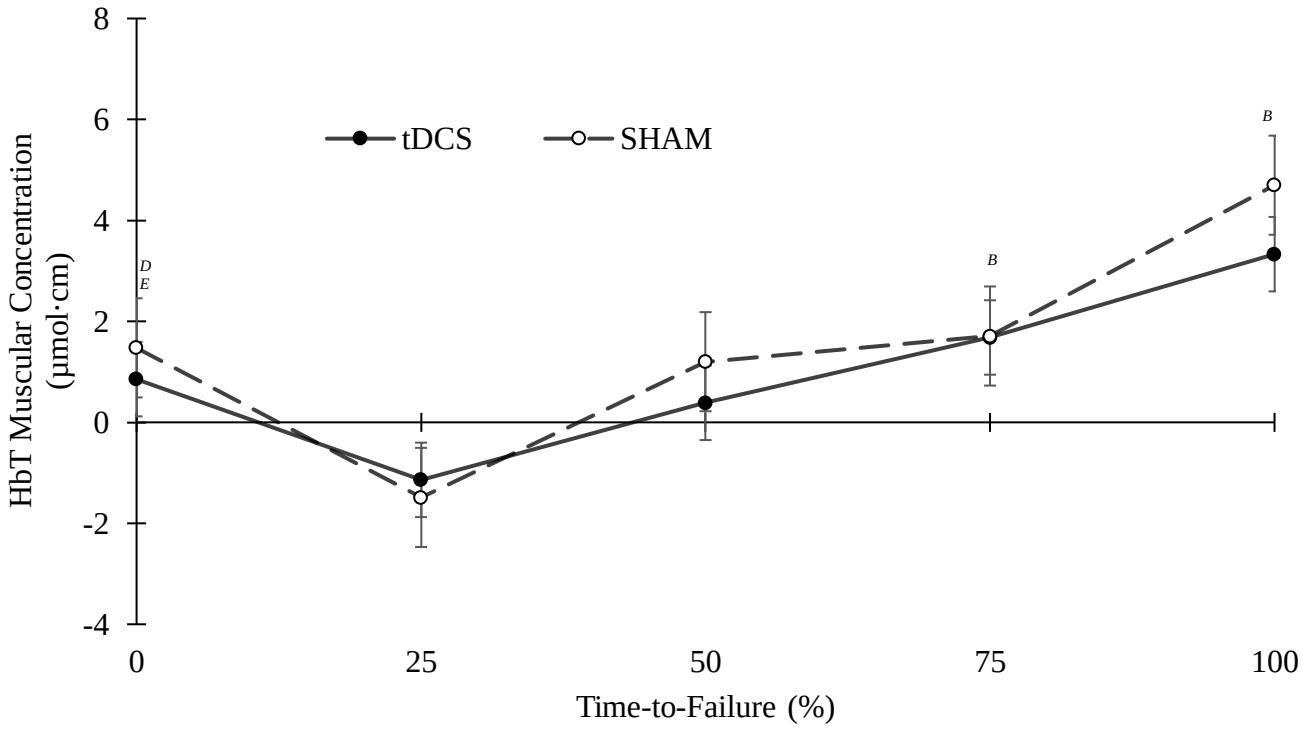

Figure 8: Total hemoglobin (oxygenated vs. deoxygenated hemoglobin) muscular concentration changes from baseline measured during handgrip time-to-failure. HbT = total hemoglobin. Data are reported as mean ± SE. *$p < 0.05$ indicates a significant main effect for time. Total hemoglobin different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

Recovery Maximal Voluntary Contraction

Changes in MVC post-test are illustrated in Figure 9 for descriptive purposes. The linear mixed effect model revealed no significant interaction between condition and time on recovery MVC ($p > 0.05$). There was no significant main effect of condition on recovery MVC ($p > 0.05$). There was however a significant main effect of time on recovery MVC ($p < 0.001$). Pairwise comparisons using the Bonferroni method revealed significant differences in recovery MVC between baseline – immediately after, 1-, 5-, and 10 minutes post-test, and between immediately after 1-, 5-, 10 minutes post-test (all $p < 0.001$). A summary of the multilevel model can be found in table 2.

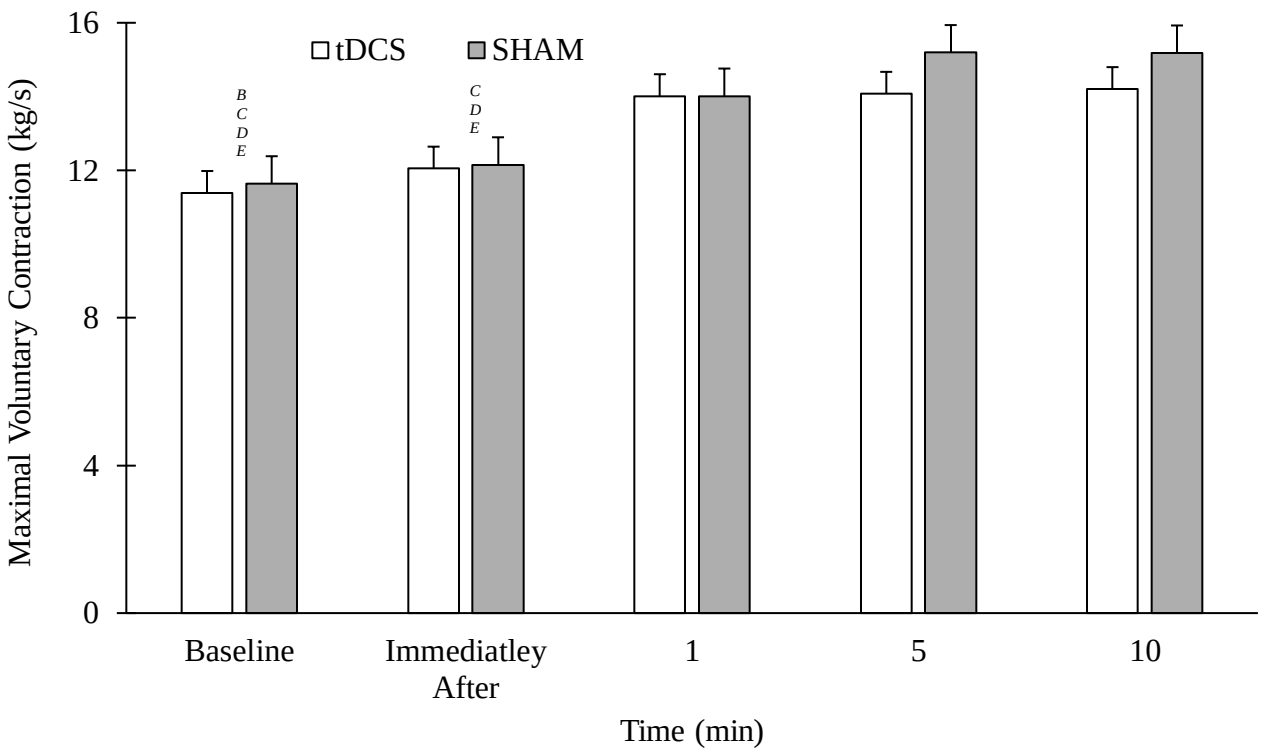

Figure 9: Alterations in maximal voluntary contraction recovery across time points. Data are reported as mean ± SD. tDCS = transcranial direct current stimulation. Maximal voluntary contraction different from 0, 25, 50, 75 and 100% (*$p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, ^{D}, and ^{E}, respectively.

Table 2: Summary of Multilevel Model.

Condition	Time (min)	β	t	df	p
tDCS	0	-4.65	-8.09	215.0028	-8.097 4.15e-14***
	1	-2.68	-4.67	215.0028	-4.673 5.22e-06***
	5	-2.62	-4.56	215.0028	-4.568 8.31e-06***
	10	-2.4	-4.14	215.002	-4.144 4.91e-05***
SHAM	0	0.53	0.65	215.0028	0.511
	1	0.43	0.53	215.0028	0.596
	5	1.54	1.9	215.0028	0.058
	10	1.32	1.61	215.0112	0.107

*******Significant difference from baseline ($p < 0.001$).

CHAPTER FIVE: DISCUSSION

The purpose of this study was to investigate the effects of tDCS delivered over the DLPFC on HGTTF, muscle oxygenation of the DLPFC and peripheral muscle oxygenation, and recovery MVC in healthy adults over 60 years of age. The key findings were: (1) a-tDCS did not improve HGTTF as compared to SHAM conditions, (2) a-tDCS did not alter central or peripheral hemodynamics, and (3) a-tDCS did not have an effect on MVC recovery post-HGTTF. These findings contribute to our understanding of the neuromodulatory effects of tDCS delivered over the DLPFC in older adults, suggesting it may not enhance physical performance or hemodynamic responses during small-muscle fatiguing tasks.

Handgrip Time-to-Failure

There was no significant difference in HGTTF across conditions. To the best of our knowledge, we are the first group to examine the effects of tDCS applied to the DLPFC on TTF in a small muscle group among healthy adults over 60 years of age. Previous researchers have focused on examinations of a-tDCS delivered over the M1 on TTF in isolated single-joint movements (i.e., elbow flexors, knee extensors) among healthy young adults (Kan et al., 2013; Muthalib et al., 2013). Our data align with previously reported findings that a-tDCS has no significant effect on time-to-fatigue in isolated, single joint movements (Kan et al., 2013; Muthalib et al., 2013). However, our results contradict previous studies showing improvements in cycling time-to-exhaustion (Etemadi et al., 2023; Lattari et al., 2018), volume load in the leg press exercise (Alix-Fages et al., 2020), and repetitions-to-failure in the bench press exercise (Lattari et al., 2020) following a-tDCS of the DLPFC.

These differences are likely due to the small muscle (i.e., FCR) utilized in the current study. During exercise, group III and IV afferents provide input to the central nervous system on contraction induced mechanical and biochemical stimuli (Amann M., 2012). Additionally, Rossman and colleagues (2013) sought to isolate group III/IV afferents to the knee extensors and compare the magnitude of peripheral fatigue following TTF of knee extensors and cycling dynamic exercise, and found a 36% increased magnitude of peripheral fatigue following TTF in knee extensors. Indicating a decrease in active muscle volume allows the central nervous system to withstand a higher level of peripheral fatigue. The use of HGTTF in the current study may not have caused enough central fatigue to demonstrate the effects of tDCS modulation. These findings provide evidence tDCS over the DLPFC may elicit ergogenic effects during large muscle group and dynamic exercise, but may have a negatable effect during small muscle mass activity.

Additionally, aging is associated with an abundance of physiological and functional impairments (McGinley et al., 2010; Zarzissi et al., 2019). However, previous researchers investigating the effects of tDCS in healthy older adults have focused on motor and cognitive functioning tasks and have shown conflicting results (Hardwick and Celnik, 2014; Flöel et al., 2014; Zhou et al., 2021). Researchers have proposed a critical threshold for peripheral fatigue, where feedback from group III/IV afferents to the central nervous system leads to decreased motor neuron output during fatiguing tasks, aiming to limit the progression of peripheral fatigue (McGinley et al., 2010; Zarzissi et al., 2019). Zarzissi and colleagues (2019) sought to determine the magnitude of the maximal level of peripheral fatigue attainable for a given task in both younger and older participants and found the peripheral fatigue threshold was higher in the young group as compared to the older group. Providing evidence aging reduces the maximal

level of peripheral fatigue tolerable and limits exercise capacity. It is possible due to the small muscle group utilized in the current study, along with the critical threshold for peripheral fatigue, exercise may have been terminated due to increased peripheral fatigue rather than centrally induced fatigue. More research is needed on the impact of a-tDCS on motor performance in healthy older adults utilizing larger muscle groups.

Central and Muscular Hemodynamics

There were no differences in HbO, HbR, and HbT between conditions. This may be due to the small muscle mass used. It is possible there would be a change in central hemodynamics if a larger muscle group was utilized as this may have been more cognitively demanding, therefore inducing central fatigue. Mean changes in HbO from baseline gradually increased from 0%, 25%, 50%, and 75% TTF, before slightly decreasing at 100% TTF. However, there were no significant differences between 75% and 100% TTF. These results agree with previous researchers investigating PFC hemodynamics following tDCS (Auten et al., 2021; Muthalib et al., 2013). Muthalib and colleagues (2021) demonstrated PFC HbO and HbR were not affected by tDCS or SHAM conditions during a submaximal sustained isometric contraction task of the elbow flexors. Previous researchers have demonstrated HbO, HbR, and HbT increase as a function of exercise intensity and duration (Giles et al., 2014). Therefore, increased exercise duration and intensity utilizing large muscle groups may fatigue the DLPFC to a point requiring neuromodulation and reveal a shift in metabolic resources to the DLPFC.

As expected, HbO gradually decreased during the TTF task and then gradually increased as exercise neared cessation. While HbR gradually increased during the TTF task and plateaued at 75% TTF in both conditions. Our results are similar to that of Auten and colleagues (2021)

who found no differences in average muscle oxygen saturation between tDCS and SHAM conditions over M1 during a 10 km self-paced time trial. These results indicate tDCS may not have an effect on peripheral hemodynamics regardless of intensity or muscle size utilized during exercise.

Recovery

Results indicated tDCS did not change the rate of recovery following the TTF task. Interestingly or group observed significant differences in post-test MVC's higher than baseline at 1-, 5-, and 10-minutes post-test. This is unexpected, as previously stated aging adults require a longer recovery period to return to baseline levels compared to their younger counterparts (Fell & Williams, 2008). Suggesting our HGTTF protocol failed to induce both central or peripheral fatigue. However, no formal measures of central or peripheral fatigue were utilized in the current study. Our findings add to the already contrasting evidence on the effects of tDCS on exercise recovery (Cogiamanian et al., 2007; Kan et al., 2013; Muthalib et al., 2013). Cogiamanian and colleagues (2007) reported a-tDCS induced a significantly lower decrease in endurance time as compared to baseline endurance time than c-tDCS or no stimulation during post-treatment sustained submaximal isometric time-to-failure task. These authors also observed a 30% increase in motor evoked potential assessed via transcranial magnetic stimulation following a-tDCS conditions, attributing the increase in endurance time to an increase in motor cortex excitability. The current study failed to provide measurements of corticospinal excitability, therefore we are unable to determine the effectiveness of the tDCS montage utilized. It is possible our tDCS montage was ineffective in producing significant changes in cortical excitability. Additionally, our group stimulated the DLPFC while previous researchers have focused on M1 (Cogiamanian

et al., 2007; Kan et al., 2013; Muthalib et al., 2013). However, due to the small muscle mass used in the current study, stimulation of the DLPFC may not have an effect on muscle performance due to an increased central nervous system tolerance of peripheral fatigue observed during isolated small muscle mass testing (Zarzissi et al., 2019). Research regarding the effects of tDCS on recovery is limited and further investigation on the effects of tDCS delivered over the DLPFC is needed.

Implications

tDCS is gaining popularity as an ergogenic aid and neurorehabilitation technique in healthy and clinical populations (Machado et al., 2019). However, results derived from studies investigating tDCS on exercise performance are hard to reproduce (Haikalis et al., 2023). Additionally, research is lacking on the use of tDCS as an ergogenic aid in healthy adults over 60 years of age. With this in mind, our findings have implications for future researchers investigating the effects of tDCS on exercise performance should look to induce central fatigue by utilizing larger muscle groups, preferably whole-body dynamic exercises or compound lifts. Furthermore, brain imaging data should be in future studies as a measure of central fatigue. Lastly, researchers should compare the effects of tDCS across all age groups.

Limitations

We implemented tDCS over the DLPFC prior to the HGTTF task. Handgrip exercise is, however, not without its limitations. Our findings related to HGTTF are limited to the small muscle mass engaged. Thus, these findings may not be entirely transferable to more dynamic exercise used in conjunction with tDCS such as bench press, leg press, and cycling, which likely

increase central fatigue to a point where neuromodulation via tDCS may be relevant. Another. key limitation to the current study was the absence of central or peripheral fatigue measurements. Additionally, the large electrode size may have had a neuromodulatory effect on brain regions surrounding the DLPFC. In conjunction with the 10/20 Electrode placement cap, the DLPFC may not have been properly stimulated.

Conclusion

tDCS over the DLPFC did not increase HGTTF in adults over 60 years of age. There were no differences in central and peripheral fatigue between tDCS and SHAM conditions. Overall, these findings provide novel insight into the neuromodulatory effects of tDCS over the DLPFC in adults over 60 years of age and serve as an important step for better guiding researchers and clinicians on the use of tDCS prior to exercise.

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APPENDIX A

IRB Approval

NORTHERN MICHIGAN UNIVERSITY

Graduate Studies and Research
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Memorandum

TO: Matt Kilgas
Yousef Qadumi
School of Health and Human Performance

Lukas Klawitter
Joshua Carlson
Eric Naugle

DATE: March 14, 2023

FROM: Lisa Schade Eckert
Dean of Graduate Studies and Research

SUBJECT: **IRB Proposal:** HS23-1371
IRB Approval Date: 3/14/2023
Proposed Project Dates: 5/1/2023-5/1/2024
"The Effect of Transcranial Direct Current Stimulation on Prefrontal Cortex Hemodynamics and Handgrip Time to Failure and Prefrontal Cortex Hemodynamics"

Your proposal "The Effect of Transcranial Direct Current Stimulation on Prefrontal Cortex Hemodynamics and Handgrip Time to Failure and Prefrontal Cortex Hemodynamics" has been approved by the NMU Institutional Review Board. Include your proposal number (HS23-1371) on all research materials and on any correspondence regarding this project.

A. If a subject suffers an injury during research, or if there is an incident of non-compliance with IRB policies and procedures, you must take immediate action to assist the subject and notify the IRB chair (dereande@nmu.edu) and NMU's IRB administrator (leckert@nmu.edu) within 48 hours. Additionally, you must complete an Unanticipated Problem or Adverse Event Form for Research Involving Human Subjects.

B. Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding. Informed consent must continue throughout the project via a dialogue between the researcher and research participant.

C. If you find that modifications of investigators, methods, or procedures are necessary, you must submit a Project Modification Form for Research Involving Human Subjects

before collecting data. Any changes or revisions to your approved research plan must be approved by the IRB prior to implementation.

Until further guidance, per CDC guidelines, the PI is responsible for obtaining signatures on the COVID-19 Researcher Agreement and Release and COVID-19 Research Participant Agreement and Release forms for any in person research and following any COVID guidelines in their research location.

All forms can be found at the NMU Human Subjects Research webpage.