

THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE
DORSOLATERAL PREFRONTAL CORTEX ON
MUSCLE FATIGUE RESISTANCE

By

Taylie Thompson Liddell

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Department of Kinesiology and Nutrition Sciences
School of Integrated Health Sciences
The Graduate College

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Taylie Thompson Liddell

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Master of Science – Kinesiology
Department of Kinesiology and Nutrition Sciences

Brach Poston, Ph.D.
Examination Committee Chair

James Navalta, Ph.D.
Examination Committee Member

Sharon Jalene, Ph.D.
Examination Committee Member

Mark Guadagnoli, Ph.D.
Graduate College Faculty Representative

Alyssa Crittenden, Ph.D.
*Vice Provost for Graduate Education &
Dean of the Graduate College*

ABSTRACT

Transcranial direct current stimulation (tDCS) delivered to the dorsolateral prefrontal cortex (DLPFC) can increase endurance time in lower body cycling tasks. The purpose was to examine the effect of DLPFC-tDCS on the time to task failure (TTF) of a fatiguing contraction performed by hand muscles. The study used a double-blind, randomized, SHAM-controlled, crossover design. Participants completed two experimental sessions on separate days with a washout between sessions. All facets of the experiments were identical except the stimulation condition (DLPFC-tDCS or SHAM) that was given concurrent with the fatiguing contraction. The fatiguing contraction involved gripping a manipulandum with the index finger and thumb using a precision grip and matching an isometric target equal to 15% of the maximum voluntary contraction (MVC) for as long as possible until task failure. The main findings were that TTF and fatigue index did not differ between the DLPFC-tDCS and SHAM conditions. Furthermore, there was no significant differences during the fatiguing contractions in the rates of increase of electromyographic (EMG), force error, or standard deviation (SD) of force between the DLPFC-tDCS and SHAM conditions. Overall, the results indicate that application of DLPFC-tDCS does not reduce the rate of muscle fatigue development in the current task conditions.

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CHAPTER 1

INTRODUCTION

The accumulation of muscle fatigue with sustained muscle contractions or physical exercise has detrimental effects of various motor abilities such as movement skill [1] and consistency as well as muscle power and force production [2]. Accordingly, muscle fatigue is commonly defined and quantified as a reduction in power or force production capability due to physical activity [2-10]. These reductions in maximal force production result from numerous changes that occur in the central nervous system and at the level of the muscle [2, 6, 11, 12]. One prominent characteristic of muscle fatigue is that the relative contribution of these two sites to the total fatiguability measured in a particular motor task is highly dependent on the parameters of the motor task being studied [4, 5, 8, 12, 13]. In general, central nervous system processes comprise the majority of the contribution to total fatiguability in sustained low-force contractions, whereas processes occurring at the muscle level provide greater contributions during sustained or intermittent maximal or near maximal contractions [6].

The negative effects of muscle fatigue not only impact motor performance in domains such as sporting events, workplace ergonomics, military applications, and rehabilitation settings in healthy populations, but also in daily activities performed by older adults or individuals with motor disorders. Despite the recognized importance of muscle fatigue in human movement control, few interventions exist that can meaningfully reduce the rate of development of muscle fatigue to a degree that would represent significant biomedical or clinical effects [14]. While longstanding conventional training, dietary, and pharmacological interventions are effective, most are either already well-known or have the limitations such as limited efficacy, side-effects, environmental specificity, and low adherence [14]. Accordingly, there are many compelling

reasons for the development of new approaches to fatigue mitigation that are time and cost effective for practical implementation in various populations [9, 14, 15].

Muscle fatigue in almost every motor task manifests due to the simultaneous involvement numerous physiological mechanisms. For example, the primary adjustments known to occur with the progression of fatigue include increases in descending drive [2, 16], motor unit recruitment [6, 17], motor unit discharge rate variability [8], and inhibitory feedback from group III and IV muscle afferents[2] as well as concomitant declines in motor unit discharge rates [7, 8, 17] and excitatory group Ia afferent feedback [18]. Therefore, it follows that any novel modality developed to ameliorate muscle fatigue would likely need to impinge upon several different underlying processes, especially the ones the greatest influences on total fatiguability in common or important motor tasks. This could be accomplished through an intervention that could reduce the rate of development of physiological factors that limit the mitigation of muscle fatigue or may enhance normal physiological factors that act to compensation for the advancement of muscle fatigue.

Non-invasive brain stimulation (NIBS) techniques represent one type of modality that could positively impact different facets of human motor performance and several of the aforementioned processes of muscle fatigue. Over at least the past decade and a half, there has been a constantly growing interest in several types of NIBS in many different fields. In particular, transcranial direct current stimulation (tDCS) is one potential innovative intervention that has been shown improve several aspects movement control, with motor skill and learning being the most widely target motor abilities [19-26]. A typical tDCS protocol usually involves 20 minutes of stimulation with a current strength of 1-2 mA delivered to primary motor cortex (M1) simultaneous with the performance of the motor task. The motor tasks studied have most

frequently been unilateral finger sequence tasks [27] and pinch grip tasks involving hand muscle, but more complex movements such as overhand throwing have also been investigated. In these conditions, participants generally improve motor skill over the course of task practice, but these enhancements are often about 10-15% larger in magnitude under M1-tDCS than those observed from motor practice alone under SHAM stimulation [19, 24, 26, 27]. In contrast, the effects of M1-tDCS on muscle fatigue resistance have not been investigated nearly as extensively as in motor skill. Nonetheless, a reasonable number of studies have indicated that M1-tDCS displays some promise for the attenuation of muscle fatigue. In a seminal study, Cogiamanian et al. (2007) [28] demonstrated that M1-tDCS increased the isometric force endurance capabilities of the elbow flexors. Subsequently, other studies that targeting M1 with tDCS corroborated these initial findings [29, 30] and provided support for the idea that M1-tDCS could not only improve motor skill and learning, but also muscle fatigue resistance [10, 28-32].

Although M1 has been the most commonly targeted brain area in tDCS studies involving motor skill learning and muscle fatigue, other studies have applied tDCS to other motor areas such as premotor cortex, the cerebellum, and dorsolateral prefrontal cortex (DLPFC). In particular, multiple studies found that tDCS delivered over the DLPFC (hereafter referred to as DLPFC-tDCS) could increase motor skill [33, 34]. Additional studies provided evidence that DLPFC-tDCS could also increase TTF and decrease the normal progression of muscle fatigue. For example, one study found that left DLPFC-tDCS enhanced cycling time to exhaustion relative to SHAM stimulation [35]. In another small study that included 8 young adults, left DLPFC-tDCS significantly improved TTF compared to SHAM stimulation in a fatiguing isometric contraction of the knee extensors [36]. Therefore, DLPFC-tDCS appears to be a compelling, time and cost-efficient alternative modality to impact the progression of muscle

fatigue, at least in motor tasks involving the lower extremities. However, the ability of DLPFC-tDCS to increase TTF and delay the development of muscle fatigue in upper limb or hand muscles has not been established, although these muscles are generally thought to be more susceptible to tDCS compared with the muscles of the lower extremity.

The purpose was to examine the effect of DLPFC-tDCS on the time to task failure of a fatiguing contraction performed by hand muscles. It was hypothesized that: 1) DLPFC-tDCS would increase the TTF of the fatiguing contraction and decrease the fatigue index compared to SHAM stimulation; 2) the rates of increase of EMG, force error, and SD of force obtained during the fatiguing contraction would be lower in the DLPFC-tDCS condition compared to the SHAM condition; and 3) transfer of motor skill measured after the fatiguing contraction would be greater in the DLPFC-tDCS condition compared to the SHAM condition. These hypotheses were collectively based on prior fine and gross motor skill studies [33, 34] and lower body fatigue studies involving application of DLPFC-tDCS [35, 36].

CHAPTER 2

METHODS

Participants

A total of thirteen healthy adults (6 males, 7 females; \pm standard deviation age: 25.8 ± 7.2 years) provided written informed consent and participated in the study. The Edinburgh Handedness Inventory was used to confirm that all of the participants were right-handed [37]. Participants were screened to determine that did not meet the tDCS or TMS criteria for exclusion [38, 39]. Participants affirmed that they did not possess any neurological disorders, psychiatric conditions, or uncontrolled medical conditions. In addition, participants were excluded if they had a history of migraines, concussions, or seizures. All of the study procedures complied with the Declaration of Helsinki and the study was approved by the University of Nevada Las Vegas Biomedical Institutional Review Board.

Experimental Design and Procedures

A double-blind, randomized, SHAM-controlled, within-subjects crossover design was used for this study. Participants completed two experiments that were conducted seven days apart [40, 41] and at approximately the same time each day. All facets of the experiments were identical except the stimulation condition (DLPFC-tDCS or SHAM) that was given concurrent with the fatiguing contraction. The order of presentation of the experimental conditions was randomized by an investigator not involved in data collection using an online application (Research Randomizer; www.randomizer.org).

The two experimental sessions each involved the same series of experimental tasks. Prior to the fatiguing contraction the nine-hole peg test (9-HPT) and MVCs were performed followed by placement of the electrode montage. Next, either DLPFC-tDCS or SHAM stimulation was applied at rest for 3 minutes. Subsequently, the fatiguing contraction began while either DLPFC-

tDCS or SHAM continued to be applied for up to 17 more minutes. Finally, the MVCs and 9-HPT were repeated immediately after the fatiguing contraction ended (Figure 1).

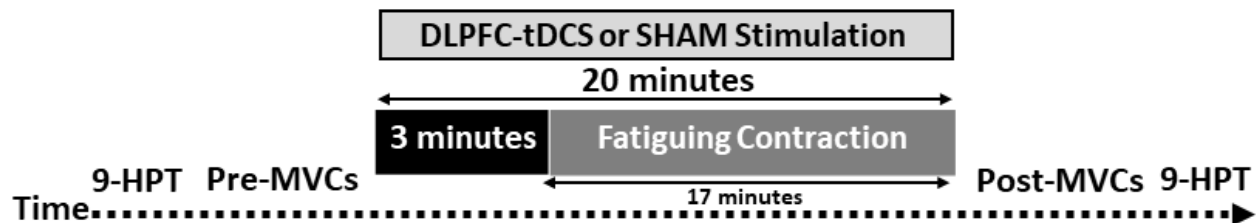


Figure 1. Schematic representation of the study design and experimental protocol.

9-HPT. Participants performed the Rolyan 9-HPT seated in front of a small table with the pegboard positioned directly in front of them to allow manipulation of the pegs. The non-dominant (left hand) was placed to the left of the pegboard and held stationary while all 9-HPT testing was performed by the right hand similar to previous methods [42]. Participants were directed to grasp the pegs with the thumb and index finger (precision grip), move them from the pegboard dish to the holes on the right side of the dish, and then move them back to the dish. In addition, participants were told to do this as fast and as accurately as possible for time. This sequence of events was repeated for a total of ten trials at the beginning and end of each experimental session.

The 9-HPT task was incorporated into the study for several reasons. It comprises one of the tests in the National Institutes of Health (NIH) motor battery toolbox [43] and therefore is a common and standard metric of manual dexterity [44]. It also is characterized by ease of administration and data can be both collected and analyzed in a short period of time. Based on these considerations, it was selected in the present study to fulfill the role of a transfer of motor skill task and thereby complement measures of force accuracy and variability attained in the

fatiguing contraction task that could all be influenced by DLPFC-tDCS. Thus, reductions in force error and force variability during the fatiguing contraction along with reductions in 9-HPT times subsequent to the fatigue task would collectively provide evidence that any effects of DLPFC-tDCS on TTF could at least partially be due to factors related to motor skill enhancement.

EMG Recording. EMG signals were recorded with two surface electrodes (3M Red Dot, Neonatal, Pre-Wired disposable electrodes) arranged in a belly tendon montage from the right first dorsal interosseus (FDI) muscle for both the MVCs and the fatiguing contraction. EMG signals acquired during the Pre-MVCs were used to normalize the EMG values obtained during the fatiguing contraction to the maximal EMG. All EMG signals were collected using hardware (1902 Amplifier and Micro 1401 analog to digital converter) from Cambridge Electronic Design in all experiments.

MVC Force Measurement. The methodology used to perform the MVCs was identical to prior studies [40, 42, 45]. In brief, participants were seated in a chair that was positioned in front of a computer monitor one meter away at eye level. The index finger and thumb assumed a precision grip and grasped a manipulandum that was located on a table to the right of participants. The index finger and thumb forces were recorded by two small force transducers (Model S215; Strain Measurement Devices; Meriden, Connecticut), which were housed on opposite sides of the manipulandum and allowed for the precision grip posture with the hand in a semi-supinated position. The wrist was set in a neutral position, the angle of elbow joint was approximately 90 degrees, and the right arm was abducted to about 45 degrees.

Participants completed three MVCs before (pre-MVCs) and after (post-MVCs) the fatiguing contraction task with a minute of rest after each MVC. The precision grip force was

displayed on the computer monitor for visual feedback in the form of a red trace that scrolled across screen with time. The instructions were to produce the maximum possible force in the minimal possible time and to maintain this maximum force for approximately five seconds until the red force trace reached the end of the screen [42, 46].

DLPFC-tDCS. Anodal tDCS was applied unilaterally to the left DLPFC via a NeuroConn DC Stimulator MR. The left DLPFC was located utilizing the Beam F3 system [47] and methods similar to a prior study [48]. This involved measurements of the taking measurements of the tragus-tragus and nasion-inion distances along with the head circumference with measuring tape. Subsequently, these values were entered into an online software application (www.clinicalresearcher.org), which provided the requisite measurements to mark the left DLPFC for electrode placement. The electrode montage arrangement, size of each the two electrodes, and parameters of tDCS were the same as used in a previous fatigue study by Angius and colleagues [35]. Accordingly, the anode was centered over the left DLPFC and consisted of a 5 x 7 cm rubber electrode placed in a saline soaked sponge. The anode was orientated so that the 7 cm sides ran anterior to posterior along the scalp. In contrast, the cathode was placed over the contralateral supraorbital region above the right eyebrow and consisted of a 5 x 5 cm rubber electrode placed in a saline soaked sponge. The anode and cathode were held in these positions with two separate rubber straps. The stimulation intensity (current strength) was 2 mA and delivered for up to a maximum of 20 minutes (see below). For the SHAM stimulation condition, the current was ramped up over a period of 10 seconds, held at 2 mA for 30 seconds, and ramped down over a period of 10 seconds according to the standard procedure used in most tDCS studies [40, 45].

Figure 1 depicts the stimulation and timing and duration relative to the execution of the fatiguing contraction. The stimulator was originally set to run for a total of 20 minutes

continuously. The first 3 minutes was given at rest [40] and then participants began the execution of the fatiguing contraction. This stimulation continued for up to 17 minutes or until task failure, whichever occurred first. Based on data from a review article, however, we did not expect participants to be able to continue the fatiguing contraction for over 17 minutes. Consistent with this expectation none of the participants achieved a TTF of 17 minutes or greater. Therefore, the total simulation time was somewhat variable across participants as in prior tDCS fatigue studies [29, 30, 40] and the tDCS device was switched off at task failure by a member of the research team. The operation of the tDCS device was carried out by a research team member who was not involved in the data collection facets of any of the experiments as described previously [40, 45, 49]. Accordingly, the study was conducted in a double-blinded fashion as the investigators that were responsible for data collection were blinded to the stimulation condition given to the participants on each of the two days.

Fatiguing Contraction. The precision grip task used for performance of the fatiguing contraction was the same as for the MVCs with the exception that the target level was set to 15% of the Pre-MVC force. The same precision grip task has also been used extensively in our prior fatigue [40] and motor skill studies [45, 46]. Accordingly, the fatiguing contraction was executed by placing the index finger and thumb on the force transducers of the manipulandum and matching the 15% MVC isometric target force for as long as possible until task failure occurred. Task failure was defined as either allowing the force to drop 10% or more for a time period of 3 seconds, not being able to maintain the required body, limb, and finger positions despite strong warnings, or a precipitous drop in force due to complete exhaustion of the involved muscles [40, 50]. The target force level of the fatiguing contraction was able to be maintained through the use of visual feedback of the force trace relative to the target force line, which was provided by a

monitor situated in front of the participant. Importantly, standardized instructions were given to match the force generated to the target force as accurately as possible at all times using the visual feedback provided until task failure.

Data Analysis

All EMG and force data in the experimental sessions were acquired utilizing custom-written scripts in the Signal software package (Cambridge Electronic Design, Cambridge UK). Offline data analysis was accomplished using additional custom-written scripts in Signal software and in the Python (Fredericksburg, Virginia, USA). The dependent variables included: TTF, fatigue index, Pre-MVC, target force, average force (*aforce*), average EMG (*aEMG*), force error, and SD of force. These dependent variables of *aforce*, *aEMG*, force error, and SD of force were acquired during the fatiguing contraction and were calculated over four equal epochs of time (E1, E2, E3, and E4), which represented 25% time segments of duration of the fatiguing contraction for each participant in each experiment.

The dependent variables were quantified according to the following approaches: 1) the TTF was determined as the total time (seconds) that the fatiguing contraction was maintained; 2) the fatigue index was determined as the percent force change from the Pre-MVC to the first post-MVC [2]; 3) the Pre-MVC was denoted as the single MVC trial with the highest force value out of the three pre-MVCs; 4) the target force was calculated as 15% of the Pre-MVC for each participant and for each of the two experiments; 5) the *aforce* was quantified as the average force produced in each time epoch of the fatiguing contraction; 6) the *aEMG* values were determined by removing the DC offset from the interference EMG, rectifying the resulting interference EMG, normalizing the values to the maximum rectified EMG of the Pre-MVC, and taking the average of the signal in each time epoch of the fatiguing contraction; 7) the force error was

quantified in the same manner as a prior fatigue study in our laboratory as well as a series of motor skill studies [40, 45, 46]. Thus, the force produced by participants was subtracted from the target force line for each sampling point. Next, the absolute values of all these differences were calculated and averaged over each entire epoch of the fatiguing contraction; and 8) the SD of force was simply calculated as the SD of the force produced by in each time epoch of the fatiguing contraction.

Statistical Analyses

Separate two-tailed paired *t*-tests were utilized to compare the Pre-MVC, target force, TTF, and fatigue index between the DLPFC-tDCS and SHAM conditions. For *a*force, *a*EMG, force error, and SD of force, a series of separate 2 *condition* (DLPFC-tDCS, SHAM) x 4 *epoch* (E1, E2, E3, E4) within-subjects ANOVAs were employed to compare the DLPFC-tDCS and SHAM stimulation conditions across the four time epochs. In contrast, a 2 *condition* (DLPFC-tDCS, SHAM) x 2 *test* (pre, post) within-subjects ANOVA was utilized to compare the 9-HPT times between the DLPFC-tDCS and SHAM conditions and across the two tests. An alpha level of $P < 0.05$ was used for all statistical tests with the exception of when adjusted by Bonferroni post hoc corrections. The effect sizes are given as Cohen's *d* (*t*-tests) and partial eta squared (ANOVAs) values. Finally, data in the figures are depicted as the means +/- the standard errors, whereas data referred to in the text are means +/- standard deviations.

CHAPTER 3

RESULTS

Pre-MVC and Target Force

The paired *t*-tests revealed that both the pre-MVC ($P = 0.462$, $d = 0.211$, Figure 2A) and target force ($P = 0.462$, $d = 0.211$, Figure 2B) were not statistically different between the DLPFC-tDCS and SHAM conditions.

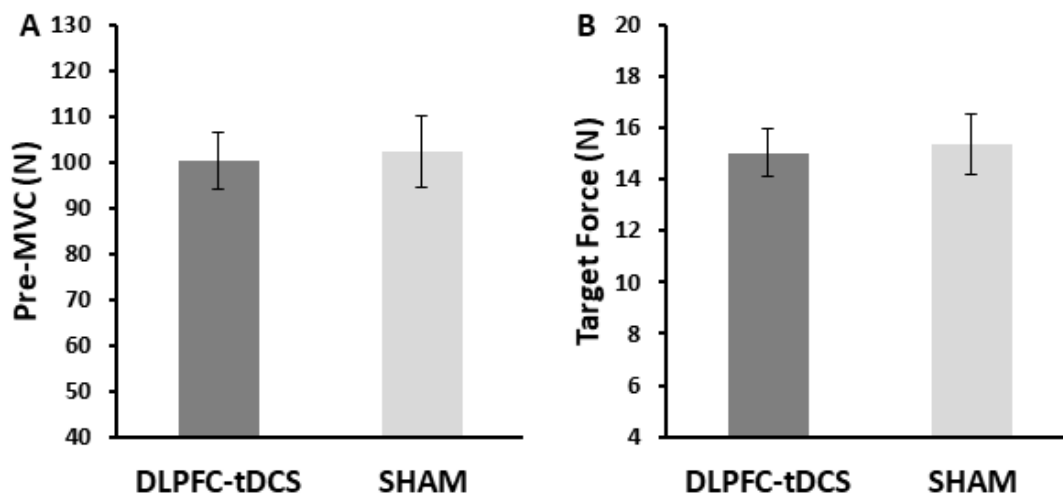


Figure 2. Pre-MVC and target force for the DLPFC-tDCS and SHAM conditions.

TTF and Fatigue Index

The paired *t*-tests revealed that both the TTF ($P = 0.995$; $d = 0.002$; Figure 3A) and the fatigue index ($P = 0.160$; $d = 0.416$; Figure 3B) were not statistically different between the DLPFC-tDCS and SHAM conditions.

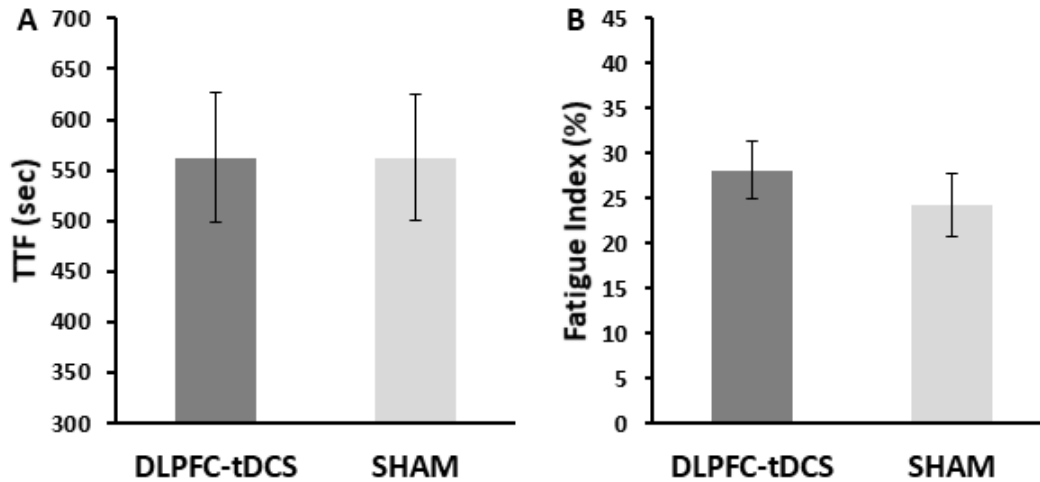


Figure 3. TTF and fatigue index for the DLPFC-tDCS and SHAM conditions.

*a*force and *a*EMG

The main effect for *condition* ($P = 0.258$; $\eta_p^2 = 0.105$) and *condition* \times *epoch* interaction ($P = 0.728$; $\eta_p^2 = 0.023$) were both non-significant for the *a*force. In contrast, there was a significant main effect for *epoch* ($P = 0.009$; $\eta_p^2 = 0.403$; (Figure 4A). Post hoc analysis of the main effect for *epoch* revealed that the *a*force for epoch 4 was significantly greater than epochs 2 ($P = 0.010$) and 3 ($P = 0.031$). Additionally, the *a*force was significantly greater for epochs 3 compared with epoch 2 ($P = 0.021$). All other pairwise comparisons were non-significant (P value range = 0.052 – 1.000). For *a*EMG, the main effect for *condition* ($P = 0.459$; $\eta_p^2 = 0.046$), main effect for *epoch* ($P = 0.079$; $\eta_p^2 = 0.216$) and *condition* \times *epoch* interaction ($P = 0.902$; $\eta_p^2 = 0.016$) were all non-significant (Figure 4B).

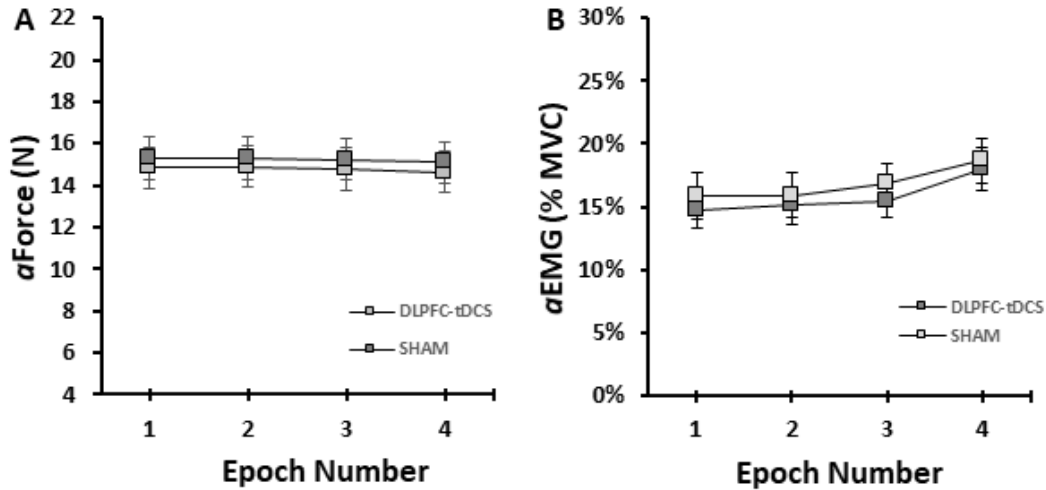


Figure 4. The α force and α EMG for the DLPFC-tDCS and SHAM conditions.

Force Error and SD of Force

The main effect for *condition* ($P = 0.220$; $\eta_p^2 = 0.122$) and the *condition* \times *epoch* interaction ($P = 0.659$; $\eta_p^2 = 0.028$) were both non-statistically significant for the force error. In contrast, there was a significant main effect for *epoch* ($P = 0.004$; $\eta_p^2 = 0.442$) as force error gradually increased over the time course of the fatiguing contractions (Figure 5A). Post hoc analysis of the main effect for *epoch* revealed that the force error for epoch 4 was significantly greater than epochs 2 ($P < 0.007$) and 3 ($P = 0.029$). Additionally, the force error was significantly greater for epoch 3 compared with epoch 2 ($P = 0.016$). Lastly, the force error was similar between epochs 1 and 2 ($P = 1.000$). For SD of force, the main effect for *condition* ($P = 0.369$; $\eta_p^2 = 0.068$), main effect for *epoch* ($P = 0.088$; $\eta_p^2 = 0.200$) and the *condition* \times *epoch* interaction ($P = 0.510$; $\eta_p^2 = 0.051$) were all non-statistically significant (Figure 5B).

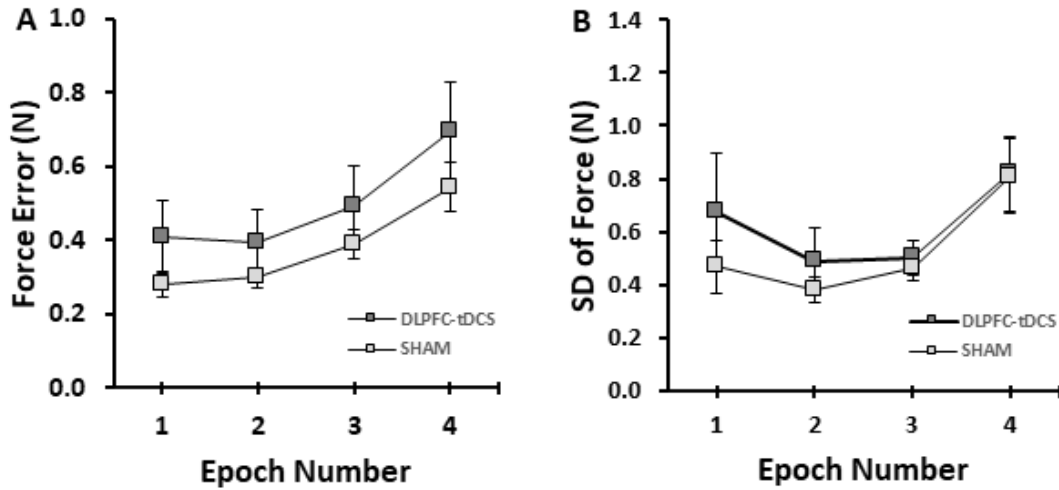


Figure 5. Force Error and SD of force for the DLPFC-tDCS and SHAM conditions.

9-HPT

For the 9-HPT times, there was a significant main effect for *condition* ($P < 0.001$; $\eta_p^2 = 0.654$), which revealed that 9-HPT times were lower in the SHAM condition compared with the DLPFC-tDCS when averaged across the pre and post-tests. The main effect for *test* ($P = 0.677$; $\eta_p^2 = 0.015$) and *condition* \times *test* interaction ($P = 0.121$; $\eta_p^2 = 0.189$) were both non-statistically significant (Figure 6).

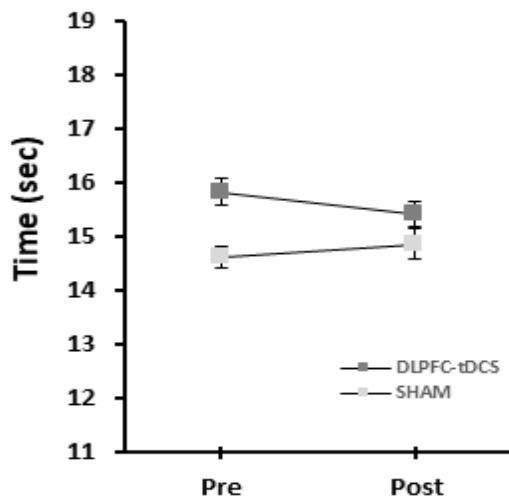


Figure 6. Pre and post 9HPT times for the DLPFC-tDCS and SHAM conditions.

CHAPTER 4

DISCUSSION

The purpose was to examine the effect of DLPFC-tDCS on the time to task failure of a fatiguing contraction performed by hand muscles. The findings indicated that DLPFC-tDCS application did not significantly increase the TTF during the fatiguing contraction or significantly decrease the fatigue index as measured by percentage decline in MVC after the fatiguing contraction ended. Similarly, DLPFC-tDCS did not slow the rate of rise of FDI *a*EMG, force error, and SD of force during the fatiguing contraction relative to SHAM stimulation. Finally, DLPFC-tDCS did not lead to any meaningful effects on the transfer of motor skill under fatigue as indicated by 9-HPT times attained after the fatiguing contraction ended. Thus, the study provided no evidence that DLPFC-tDCS attenuated any of the most common features of muscle fatigue in a precision grip task performed by the muscle so the hand.

Influence of DLPFC-tDCS application on TTF and the Fatigue Index

Previous studies have reported that DLPFC-tDCS significantly enhanced fatigue resistance in both isometric contractions and cycling tasks involving the lower limb [35, 36]. In addition, the magnitude of the effect in these studies appeared to be similar or even greater to those achieved in studies involving M1-tDCS, suggesting that DLPFC may be the brain region with most potential for the purpose of diminishing the rate of accumulation of muscle fatigue. Based on those considerations and the rationale that hand muscles may be more susceptible to NIBS compared to leg muscles [51, 52], the current study endeavored to extend these findings to the upper limb during the common experimental paradigm of a sustained submaximal isometric fatiguing contraction [2, 7, 10] utilizing a precision grip task involving primarily the index finger and thumb muscles. Contrary to the original hypotheses, the TTF for the DLPFC-tDCS condition

and the SHAM condition were almost exactly the same (562 ± 221 vs 563 ± 217 seconds, respectively). The fatigue index values displayed the same pattern of results with the DLPFC condition demonstrating a decline in MVC after the fatiguing contraction of $28 \pm 11\%$ whereas the value for the SHAM condition was $24 \pm 12\%$, differences that were also far from achieving statistical significance. These strikingly similar outcomes not only strongly suggest that DLPFC-tDCS had no influence on behavior measures of muscle fatigue, but also was extremely unlikely to have differentially influenced any of the underlying physiological manifestations of muscle fatigue relative to SHAM stimulation. Importantly, these findings were accompanied by a lack of statistically significant difference between stimulation conditions in the pre-MVCs conducted prior to the fatiguing contractions in each experiment. Since the target force levels in each experiment were set to 15% of the pre-MVC, the target forces were also similar for the DLPFC-tDCS and SHAM conditions. Thus, these related outcomes removed the potentially confounding effects of differing fatiguing contraction target force levels and the associated differences in energy expenditure that initial task conditions would have had on physiological adjustments during the fatiguing contractions. Accordingly, the *a*force produced during the fatiguing contractions was similar for the two conditions, which also served as a control to confirm that any differences in TTF and indicated that the participants performed the task as directed. Thus, if differences in TTF had been present, they could have been attributed to the stimulation condition and not random variations in Pre-MVCs between experiments or the unintentional systematic production of lower target forces in one stimulation condition.

The TTF and fatigue index results in the present study are not consistent with the majority of the available studies in the literature involving several interrelated lines of research. Most specifically, they are in contrast to lower body studies performed by Angius and colleagues

who reported that DLPFC improved TTF in a submaximal isometric contraction of the knee extensors and time to exhaustion in a lower body cycling task [35, 36]. The outcomes are also in opposition to DLPFC-tDCS studies which have found significant augmentations in motor skill acquisition [33, 34]. Furthermore, the findings differ from the balance of the literature that have involved M1-tDCS and muscle fatigue, many of which utilized the biceps or hand muscles [28-32, 53, 54]. The reasons for the conflicting results in regard to TTF and fatigue index in the current study are difficult to determine, but are likely some combination of the differences in research methodology, the motor task involved, and interindividual differences in response to tDCS.

Despite the aforementioned inconsistencies of the findings with the majority of the research on related topics, the present findings agree with a number of studies that have also failed to find significant effects of tDCS on the ability to resist muscle fatigue. Although in the minority, there are a relatively significant number of that have utilized various types of motor tasks which have reported similar negative findings to the current study [55-60]. These studies caution against the common belief that tDCS displays consistent and reliable effects on various aspects of motor performance including fatigue. In fact, a recent review article provided several arguments which highlighted the contradictory results in the tDCS literature. The main conclusions were that despite many positive studies the variability of results across studies raise considerable doubts on the utility of tDCS to mitigate fatigue. In addition, the wide range of stimulation and task parameters employed in these studies (brain area targeted, current strength, motor task, timing) coupled with the increasingly important consideration of interindividual susceptibility to tDCS due to anatomical and physiological factors were arguments that further questioned tDCS effectiveness. Some of these assertions are illustrated by examining two

separate studies with divergent results performed by the same prominent fatigue research group [53, 57]. Taken together, the main findings of the present study support the contentions that tDCS may not be as effective in ameliorating the development of fatigue in motor tasks as initial studies implied. This notion is further supported by other review articles and meta-analyses which concluded that although the majority of available literature has documented significant tDCS effects on muscle fatigue the overall effect sizes are small to moderate [31, 32, 54].

Rates of Increase of *a*EMG Activity and Force Measurements during Muscle Fatigue

A common finding in virtually all sustained, submaximal isometric fatiguing contractions is that the *a*EMG activity, force error, and SD of force progressively increase as a function of time as fatigue accumulates. Crucially, however, if differences are observed between matched conditions in isometric fatiguing contractions, such as when comparing force and position tasks [8, 13], the rates of increase in EMG and force variability would also differ across condition. Specifically, the TTF should be significantly shorter in the condition where EMG activity of the involved muscles and force variability show significantly greater rates of rise. In addition, the shorter TTF would be accompanied by interrelated physiological adjustments such as a more rapid recruitment of the motor unit pool, decreases in discharge rate of some of the active motor units, increased perceived exertion, increased heart rate and mean arterial pressure, and heightened inhibitory afferent feedback.

The current results, however, displayed none of the above characteristics for any of the variables recorded during the fatiguing contraction. The rates of increase in *a*EMG, force, error and force variability were not statistically different between the DLPFC-tDCS condition and the SHAM condition and therefore represented another set of findings that did not align with one of the original hypotheses. Accordingly, it is extremely unlikely that much more difficult

physiological measurements to record such as voluntary activation, motor unit discharge rates, increased motor unit recruitment, and group III and IV afferent feedback differed between the two stimulation conditions. This is because the measures of *a*EMG and force variability employed in the study generally reflect these underlying mechanisms, although they are relatively basic, indirect, and imprecise metrics in comparison [2, 4, 6, 7]. While the *a*EMG, force error, SD of force did increase gradually throughout the fatiguing contractions independent of stimulation condition, these observations were fully expected and not interesting due to the lack of differences in the much more critical comparison between the DLPFC-tDCS and SHAM conditions. Taken together, the above lines of reasoning and current findings strongly suggest that the general tDCS candidate mechanisms of action that could underlie fatigue attenuation put forward in a recent review of increases in output from M1, motor skill, or pain tolerance were likely to have been induced by DLPFC-tDCS in the current circumstances. This is because these mechanisms would have also almost surely been reflected by differences in the TTF, *a*EMG, force error, and SD of force measurements between stimulation conditions.

Study Limitations and Possible Reasons for Failure of DLPFC-tDCS to Influence Fatigue

The study had several limitations that should be addressed which are also likely to be highly interrelated with the potential explanations for the lack of ability of DLPFC-tDCS to significantly influence muscle fatigue. Some of these limitations are inherent to most tDCS studies, whereas others are likely more specific to the details of the current study. Similarly, the possible reasons for the absence of significant DLPFC-tDCS effects are among the most typically cited when the results of tDCS studies are not consistent with the positive results indicated by the preponderance of the literature. Briefly, one limitation of the study would be the combination of the experimental paradigm (sustained submaximal isometric contraction) and the

model muscle group (hand muscles) utilized. While this experimental model the purposes of providing strict experimental control and easy comparisons to many prior fatigue studies, it is acknowledged that it could have low functional relevance and generalize poorly to anisometric contractions [7], multi-joint motor tasks [61], or higher intensity contractions [62-67]. Another aspect of the experimental design that could have not been optimal was delivering the DLPFC during versus before performance of the fatiguing contraction. Accordingly, this relative timing delivered positive results [28, 31, 32, 35, 36, 54] in many previous studies, but others have achieved similar results with concurrent stimulation, at least with M1-tDCS [29, 30]. Finally, DLPFC tDCS may be more likely to exert effects in less trained populations such as older adults or individuals with motor disorders characterized by excessive fatigue. The sample of active young adults in the present study may have induced ceiling effects [68-71] as shown in various motor skill studies involving tDCS of different brain regions. Overall, the reasons responsible for the conflicting and variable effects of tDCS on muscle fatigue across studies and likely even between individuals will require much more research involving concurrent behavior and sophisticated physiological measurements to elucidate.

Conclusions

In summary, application of DLPFC-tDCS neither increased the TTF during the fatiguing contraction nor positively influenced the fatigue index as measured by percentage decline in MVC after the fatiguing contraction ended. Furthermore, DLPFC-tDCS did not slow the rate of rise of FDI *a*EMG, force error, and SD of force during the fatiguing contraction relative to SHAM stimulation. Finally, DLPFC-tDCS did not lead to any meaningful effects on the transfer of motor skill under fatigue. Thus, the study provided no evidence that DLPFC-tDCS is an effective intervention to attenuate any of the most common metrics of muscle fatigue, at least in

the common sustained submaximal isometric contraction experimental model. Although this model allows strict experimental control, it bears limited resemblance to many real-world motor tasks, which means the current results should be interpreted with caution and may not directly extend to other types of motor tasks. Overall, the conflicting data in the literature on the efficacy of DLPFC-tDCS for the mitigation of muscle fatigue in different motor tasks warrants future research to elucidate the mechanisms underlying the heterogenous results and to determine the circumstances in which application of DLPFC-tDCS may be most useful to enhance motor performance.

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CURRICULUM VITAE

Taylie Liddell

Current Contact Information
4505 South Maryland Parkway
Las Vegas, NV 89165
Email: taylieliddell@yahoo.com

Education

2022 B.S. Kinesiology

Department of Kinesiology
University of Nevada – Las Vegas
GPA: 3.9

Honors and Awards

1. 2018-2022 Dean's Honor List
2. 2022 Graduated Cum Laude
3. 2020-2023 Captain of UNLV soccer team

Certifications

1. Certified Personal Trainer (CPT) – American Council of Exercise