# THE EFFECT OF DUAL SOURCE PREMOTOR CORTEX TRANSCRANIAL DIRECT CURRENT STIMULATION ON MUSCLE FATIGUE IN HAND MUSCLES

By

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ABSTRACT

Single source transcranial direct current stimulation (tDCS) has been shown to increase the time to task failure (TTF) fatiguing contractions when applied to the dorsolateral prefrontal cortex (DLPFC) and to the primary motor cortex (M1). The primary purpose was to determine whether dual source tDCS delivered bilaterally over the premotor cortices (pmc-tDCS) could increase the TTF of a fatiguing contraction performed by hand muscles. A double-blind, randomized, SHAM-controlled, crossover design was used for this study with each participant performing two experimental sessions held on separate days a week apart. The only difference between the two sessions was the type of stimulation (pmc-tDCS or SHAM; counterbalanced) applied concurrent with the fatiguing contraction. In each experiment, the fatiguing contraction was performed by gripping a manipulandum with the index finger and thumb. This was accomplished by 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: 1) both the TTF and the percentage decline in MVC force did not significantly differ between the pmc-tDCS and SHAM conditions; 2) the rates of increase in electromyographic (EMG) activity, force error, and standard deviation (SD) of force were not significantly different between the pre-tDCS and SHAM conditions; and 3) transfer of motor skill under fatigue was similar between the two stimulation conditions. Collectively, these results suggest that pmc-tDCS does not decrease the rate of muscle fatigue during a sustained isometric contraction of the muscles of the hand.

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# CHAPTER 1

# INTRODUCTION

The phenomenon of muscle fatigue begins to manifest within a few seconds following the onset of exercise and develops progressively if the exercise is sustained. The presence of muscle fatigue negatively impacts all motor abilities including but not limited to movement accuracy, motor output variability, and maximum force production. Accordingly, muscle fatigue is defined as a temporary decline in the maximal voluntary contraction (MVC) force production capability of muscle due to exercise [1-8]. Fatigue does not have a single cause and arises due to adjustments that take place within both the central nervous system (central fatigue) [1, 5, 9, 10] and at the muscle level (peripheral fatigue). Thus, the total fatiguability observed in a given motor task is almost always some weighted contribution from a number of individual elements within each of these two overall sites and depends on the characteristics of the motor task [3, 4, 7, 10, 11]. For instance, the most common experimental model for studying muscle fatigue involves the performance of a unilateral sustained submaximal (e.g. 15-35% of MVC) isometric contraction with upper limb muscles. In these experimental circumstances, supraspinal mechanisms alone account for about 50-65% of the total fatiguability observed [5], which would have implications for interventions that could exert effects on supraspinal sites.

While many of the factors and underlying physiological mechanisms that contribute to fatigue have been identified over many decades of research, a remarkably small number of means have been devised that can significantly counteract the acute negative influences of fatigue on motor performance [12]. Goal-orientated exercise programs utilizing the training principles of specificity and progressive overload represent the foundation of developing resistance to muscle fatigue and should convey the most benefits if implemented intelligently

and consistently. Beyond established training methods, a number of nutritional, dietary supplement, pharmaceutical, and other nonmedication-based interventions have been studied. However, almost all of these have been either been ineffective, induced only small effects on fatigue, or work only in specific circumstances (e.g. sleep deprivation, high altitude, hot environment, long duration exercise, etc) [12]. Therefore, novel alternative strategies that can significantly impact the progression of muscle fatigue would be extremely valuable in many different settings and populations [8, 12, 13].

Any intervention directed towards reducing the effects of muscle fatigue on measures of motor performance would almost certainly need to directly target at least a few of the major physiological adjustments that occur as fatigue develops during exercise. For example, during a sustained submaximal isometric contraction the discharge rate of many of the initially active motor units decreases [1, 6, 14]. Therefore, initially unrecruited higher threshold motor units have to be gradually recruited to maintain the target force and to continue performing the task [1, 5-7]. This additional recruitment of larger motor units is accompanied by increases in force error (decreased force accuracy) relative to the target force and increases in the standard deviation (SD) of force produced. These outcomes could contribute to greater expenditures of energy to correct the larger deviations in force around the target [15] and further exacerbate the progression of fatigue. Another major physiological adjustment during fatigue is the heightened activity of group III and IV afferents, which are activated by mechanical events, temperature, pain, and metabolic stimuli such as muscle metabolism by-products (e.g. lactate, potassium ions, bradykinin, arachidonic acid and others). Group III and IV afferent feedback inhibits motor output during fatigue in at least three ways including direct inhibition of motor neurons [1],

presynaptic inhibition of Ia afferent terminal input onto motor neurons, and inhibitory projections to supraspinal sites [4, 5, 16, 17].

Transcranial direct current stimulation (tDCS) is a neuromodulatory tool that could represent intervention class that serve as an adjunct to existing fatigue mitigation practices and impact some of the major aforementioned physiological processes involved in fatigue development. Accordingly, tDCS appears to be the most effective and the most practical non-invasive brain stimulation technique for improving various motor abilities [18-25], especially motor skill acquisition and learning. The most common set of findings are that a single 10 to 20-minute application of anodal tDCS applied unilaterally to the primary motor cortex (M1) before or during motor practice [18, 23, 25, 26] enhances cortical excitability (~10-40%) motor skill acquisition (~10-15%) compared to practice alone (SHAM stimulation). In addition, a significant number of studies using similar parameters of tDCS application have reported increases in the TTF (time to task failure) during submaximal isometric contractions or endurance performance in cycling tasks [27-32].

The standard tDCS electrode montage used in the above studies involved placement of the cathode over the supraorbital (SO) and the anode over the contralateral M1 and therefore is termed the SO-M1 electrode montage. However, even early very early studies sought alternative electrode arrangements that could be more effective. In 2008, Vines et al. [33] reported that a bihemispheric montage with the cathode placed over the dominant M1 and the anode over the non-dominant M1 improved a finger sequencing motor task to a greater extent than both a SO-M1 electrode montage and SHAM stimulation. Additional individual studies and a systematic review and meta-analysis mainly confirmed these results, although the mechanisms of remain somewhat controversial [33-36]. Over the past several years, the idea of bihemispheric

stimulation has been extended and modified using novel dual source stimulation paradigms where either two separate tDCS devices or a multi-channel stimulator were used to simultaneously target bilateral homologous brain areas or two different brain areas. For example, a study by Naros et al. (2016) [34] demonstrated that both bihemispheric tDCS and dual source M1-tDCS targeting both M1s with separate SO-M1 electrode montages enhanced motor skill in an arm movement task to a greater degree than the standard SO-M1 electrode montage [34]. In addition, a more recent study reported that dual source tDCS applied bilaterally to both premotor cortices (hereafter termed pmc-tDCS) improved muscle activation, motor coordination, and force production in an array of multi-joint motor actions in gymnasts [37]. Furthermore, this same study found that an analogous dual source bilateral electrode montage applied to the cerebellar cortices resulted in similar results. Overall, the aforementioned bihemispheric and especially dual source bilateral electrode montages effects on various motor abilities strongly imply that such approaches could also be more efficacious as a muscle fatigue intervention compared with the SO-M1 montage used in prior fatigue studies.

The primary purpose was to determine whether dual source tDCS delivered bilaterally over the premotor cortices (pmc-tDCS) could increase the TTF of a fatiguing contraction performed by hand muscles. The secondary purpose was to examine some of the neural mechanisms that may underlie any observed increases in TTF due to pmc-tDCS. It was hypothesized that pmc-tDCS application would increase the TTF of the fatiguing contraction and decrease the fatigue index compared to SHAM stimulation. In addition, it was predicted that EMG activity, force error, and SD of force would display a lower rate of increase during the fatiguing contraction in the pmc-tDCS condition compared to the SHAM stimulation condition. Finally, it was anticipated that pmc-tDCS would lead to a higher transfer of motor skill in the

fatigued state following the fatiguing contraction. Collectively, these hypotheses were based on s previous dorsolateral prefrontal cortex (DLPFC) and unilateral SO-M1 electrode montage fatigue studies, premotor cortex tDCS skill studies, the overall superiority of bihemispheric montages, and on recent study that found that dual source pmc-tDCS increased motor coordination and force production in trained gymnasts [33-37].

# CHAPTER 2

# METHODS

## Participants

A total of 13 healthy adults (8 males, 5 females; average age: 28.1 ± 7.5 years) volunteers provided informed consent and completed the study. Participants were all right-handed according to the Edinburgh Handedness Inventory [38] with an average laterality quotient of 0.89 ± 0.17. Participants reported that they did not have any neurological disorders, psychiatric conditions, or uncontrolled medical conditions. In addition, participants were excluded if they had a history of concussions, migraines, or seizures. Finally, screening was done to confirm that participants did not meet the tDCS or TMS international exclusion criteria [39, 40]. The study was approved by the Institutional Review Board at the University of Nevada, Las Vegas and all procedures aligned with the Declaration of Helsinki.

## Experimental Design and Procedures

A double-blind, randomized, SHAM-controlled, crossover design was used for this study with each participant performing two experimental sessions held on separate days a week apart [15, 41]. Thus, the only difference between the two sessions was the type of stimulation (pmc-tDCS or SHAM; counterbalanced) applied concurrent with the fatiguing contraction. The order of the two experimental conditions assigned to the participants was randomized using Research Randomizer (www.randomizer.org) by an investigator who was not involved in data collection. The within-subjects design was chosen to eliminate the numerous interindividual differences that can influence the susceptibility and response to tDCS (for reviews see [42, 43]) and due to the greater statistical power associated with within-subjects versus between-subjects designs [44].

Participants were required to complete a series of experimental tasks in the order prescribed: 1) pre-9-HPT; 2) motor “hotspot” localization for the left and right first dorsal

interosseus (FDI) muscles; 3) resting motor threshold (RMT) quantification for the right FDI muscle; 4) pre-MVCs; 5) fatiguing contraction performed with either pmc-tDCS or SHAM stimulation applied for up to a total of 20 minutes (three minutes before and up to 17 minutes concurrent with the task); 6) post-MVCs; and 7) post-9-HPT. This experimental protocol is depicted below in schematic form (Figure 1).

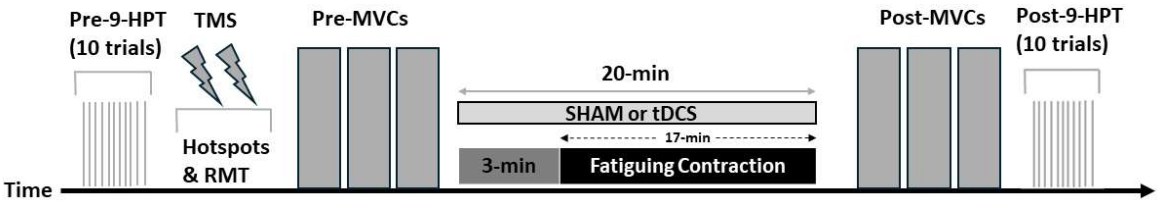


**Figure 1.** Schematic of the study protocol. Participants performed a pmc-tDCS session and a SHAM session in a counterbalanced order on separate days a week apart. Participants performed a sustained submaximal isometric fatiguing contraction with the right hand using a precision grip while either pmc-tDCS or SHAM stimulation was applied. TMS testing was performed before the fatiguing contraction to identify the FDI motor hotspots of each hand. In contrast, 9-HPT and MVC testing was performed both before and after the fatiguing contraction task.

*9-HPT.* Each experimental session began and ended with the performance of the Rolyan 9-HPT. This motor task is an item included within the National Institutes of Health (NIH) motor battery toolbox [45] and is widely used test of manual dexterity [46] as it is quick and easy to administer. In the current study, it was included to serve as a motor skill transfer task. Specifically, it was used to determine if any increases in force accuracy measures in the fatiguing contraction precision grip task would generalize to the 9-HPT performed after the fatiguing contraction and not under stimulation. Therefore, it would provide an additional accuracy

measure that could lend additional evidence that any TTF increases due to pmc-tDCS could have been partially mediated via motor skill increases.

All of the 9-HPT performed before and after the fatiguing contraction were carried out with the right hand/arm system according to previously described methods [46]. Task performances involved reaching and grasping the 9 individual pegs in succession with a precision grip, moving them to the 9 target holes, and moving them back to the dish. Participants were directed to complete this series of steps as fast and as accurately as possible. This process was completed for a total of 10 trials at the beginning (pre-9-HPT) and end (post-9-HPT) of the experiment.

*TMS Measurements and EMG Recording*. TMS was used to identify the sites for pmc-tDCS electrode placement and to measure baseline cortical excitability in each of the experimental sessions. A Magstim $200^2$ device with a figure-eight double 70 mm remote control coil was utilized to deliver single TMS pulses to the left and right M1s to elicit motor evoked potentials (MEPs) in the contralateral right and left FDI muscles, respectively. The TMS coil was pressed against the scalp and orientated tangentially to it so that the coil handle was pointed backwards and laterally at a 45-degree angle to the midline. MEPs were recorded using surface EMG electrodes that were arranged in a belly tendon montage on each of the two FDI muscles. To localize the FDI motor "hotspots", a series of TMS pulses were delivered to the hand area of each M1 until the scalp location which provided the greatest MEPs for a given stimulation intensity was identified. This spot was marked with a temporary marker and a second spot was marked at a distance of 2.5 cm anterior to the M1 hotspot and used later for the placement of the pmc-tDCS anodes [37]. Next, RMT was quantified in the right FDI using common methodology [47]. RMT measurements were obtained because previous research has suggested that RMT

values may be associated with the propensity for an individual to respond to tDCS application [48, 49]. In addition, RMT provided a basic measure of baseline cortical excitability on each of the two days before the stimulation and fatiguing contraction were performed.

*MVC Force Measurement*. Participants performed the MVC task using the same methodology, experimental arrangement, and precision grip task described in previous studies [15, 50, 51]. Participants were seated in a chair with the right arm abducted to ~45° with the elbow and forearm placed on a table surface. The elbow angle was ~90°, the wrist in neutral, the hand semi-supinated, and the index finger and thumb orientated in a precision grip posture. The forces produced by the index finger and thumb in the precision grip were obtained by two separate force transducers (Model S215; Strain Measurement Devices; Meriden, Connecticut) that were situated on either side of a custom-made grip manipulandum that was mounted on the table. These forces were summed online by the data collection software and the total force was displayed as a red trace that scrolled across a computer monitor located in front of the participants. For the MVC trials, participants were told to generate their maximum possible force in the shortest time possible and to maintain the maximum for about five seconds [51, 52]. A total of three MVC trials were executed both before (pre-MVCs) and immediately after (post-MVCs) the fatiguing contraction. A rest period of one minute was imposed between trials in the pre- and post-MVC testing. The MVC with the greatest force denoted as the pre-MVC and this value was used to calculate target force of 15% of MVC for the fatiguing contraction in each experimental session. The post-MVCs were performed immediately after task failure of the fatiguing contraction, which ended up being about 10-20 seconds post-contraction due to the need to reset the data collection system for MVC collection.

*PMC-tDCS.* Dual source tDCS was delivered bilaterally to the premotor cortices using two separate NeuroConn DC Stimulators with an identical electrode montage arrangement as Anoshiravani et al. (2023) [37]. Thus, one electrode pair comprising a cathode and anode from one of the stimulators was placed over the left prefrontal lobe (Fp1) and the left premotor cortex, respectively. Analogously, the cathode and the anode of the second electrode pair connected to the second stimulator were placed over the right prefrontal lobe (Fp2) and the right premotor cortex. Presumably, this dual anodal pmc-tDCS electrode montage should elicit increases in excitability of both the left and right premotor cortices. The Fp1 and Fp2 locations were determined using the 10-20 International EEG System, whereas the left and right premotor cortex locations were determined by taking a distance of 2.5 cm anterior to the previously identified FDI motor hotspots. All four electrodes were identical, composed of rubber, measured 5 x 7 cm, encased in saline soaked sponges, held in place by rubber straps, and were orientated with the 7 cm sides arranged in the anterior to posterior direction. The current strength was set to 2 mA for both stimulators and applied for up to 20 minutes (see below). SHAM stimulation was applied according to standard procedures [15, 50] and involved ramping the current up over 10 seconds, holding it constant at 2 mA for 30 seconds, and ramping it back down over 10 seconds for both stimulators.

The timing and duration of the stimulation in respect to the performance of the timing fatiguing contraction is shown in Figure 1. First, the stimulation time of both devices was set to 20 minutes and the first 3 minutes of stimulation were given at rest [15]. Second, the fatiguing contraction was commenced at this 3-minute demarcation time. Third, the stimulators were allowed to run for 17 minutes or until task failure, at which time they were switched off by an investigator. Since no participants exhibited a TTF greater than 17 minutes, the total simulation

time was somewhat variable across participants as in previous studies [31, 32]. The application of either pmc-tDCS or SHAM stimulation through operation of the devices was undertaken by an investigator who did not take part in the data collection as detailed in our previous studies [15, 50, 53]. Accordingly, investigators who conducted the data collection aspect of the experiments were blinded to the experimental condition.

*Fatiguing Contraction Task.* The experimental arrangement for the precision grip task implemented in the fatiguing contraction was the same as that used during the MVC task. In addition, it was identical to the precision grip task utilized in a previous fatigue study [15] as well as prior motor skill [50, 52] studies. Accordingly, the fatiguing contraction was performed by gripping the force transducer instrumented manipulandum with the precision grip and matching an isometric target force equal to 15% of the Pre-MVC force for as long as possible until task failure. The target force template was displayed as a black horizontal line on a monitor located about 1 meter in front of the participant at eye level. Participants were given strict instructions to match their precision grip force (red trace) as accurately as possible to the horizontal target force line. In addition, a second black horizontal line corresponding to a force level 10% below the target force line was displayed. Participants were told to endeavor to never allow their force to fall below that line if possible and to immediately correct (increase) the force in this case. The total time that the target force could be sustained within the constraints of the task (termination criteria) was quantified as the TTF of the fatiguing contraction. The termination criteria [15, 54] included: 1) force dropping and remaining below the 10% threshold for greater than 3 seconds; 2) an inability to sustain the requisite hand, arm, or body position despite strong verbal warnings; and 3) volitional cessation of the contraction, which is almost always the most

common of the three-termination criterion responsible for task failure in isometric fatiguing contractions studies [15].

## Data Analysis

The Signal (CED, Cambridge UK) software system was used for data collection in the experimental sessions. Offline analyses of data were performed by both custom-written scripts in signal and in the Python (Fredericksburg, Virginia, USA) programming language. The primary outcome measures were TTF and the fatigue index, whereas the secondary dependent variables were the RMT, Pre-MVC force, and target force. In addition, the average force (*a*force), average EMG (*a*EMG), force error, and SD of force obtained during the fatiguing contractions were also considered secondary dependent variables. These variables were quantified over each of four quartiles of time, which were denoted as Q1, Q2, Q3, and Q4 and represented segments of 25% of the fatiguing contraction duration.

The dependent variables were quantified as follows: 1) TTF: the time in seconds that the fatiguing contraction could be sustained until a criterion of task termination criteria was met; 2) fatigue index: the percent change between the Pre-MVC and the first post-MVC executed after the fatiguing contraction had ended [1]; 3) RMT: the lowest stimulus intensity (% MSO) that could elicit MEP amplitudes of $\geq$ 50 μV in a minimum of 5 out of 10 successive trials in the right FDI muscle; 4) Pre-MVC: the MVC trial with the highest force value among the three pre-MVCs; 5) target force: 15% of the Pre-MVC force; 6) *a*force; the mean force produced in the precision grip in each of the four time quartiles during the fatiguing contraction; 7) *a*EMG: the interference EMG signal of the right FDI was full wave rectified, normalized to the Pre-MVC maximum rectified EMG, and the average was obtained over each of the four time quartiles

during the fatiguing contraction; and 8) force error: the absolute difference in force between force produced and the target force template line was calculated at each sampling point and averaged over each of the four time quartiles during the fatiguing contraction as done in a previous fatigue study and motor skill studies [15, 50, 52]; and 8) SD of force: the SD of the force produced over each of the four time quartiles during the fatiguing contraction.

## Statistical Analyses

A series of separate two-tailed paired *t*-tests were used to compare the dependent variables of TTF, percentage decline in MVC, RMT, Pre-MVC, and target force between the pmc-tDCS and SHAM stimulation conditions. In contrast, a series of 2 *condition* (pmc-tDCS, SHAM) x 4 *quartile* (Q1, Q2, Q3, Q4) within-subjects ANOVAs were used compare the dependent variables of *a*force, *a*EMG, force error, and SD of force between the pmc-tDCS and SHAM stimulation conditions across the four-time quartiles. Finally, a 2 *condition* (pmc-tDCS, SHAM) x 2 *test* (pre, post) within-subjects ANOVA was used to compare 9-HPT times between the pmc-tDCS and SHAM stimulation conditions and across the two tests. A significance level of $P < 0.05$ was utilized for all of the aforementioned statistical tests, except when alpha levels were adjusted by Bonferroni post hoc corrections when appropriate. Effect sizes are reported as Cohen's d for the *t*-tests and partial eta squared for the ANOVAs. The data are shown as the means +/- the standard errors in all of the figures.

# CHAPTER 3

# RESULTS

## RMT, Pre-MVC, and Target Force

Separate paired *t*-tests indicated that the RMT ($P = 0.695$, d = 0.111, Figure 2A), pre-MVC ($P = 0.528$, d = 0.180, Figure 2B), and target force ($P = 0.528$, d = 0.180, Figure 2C) were all not statistically different between the pmc-tDCS and SHAM conditions.

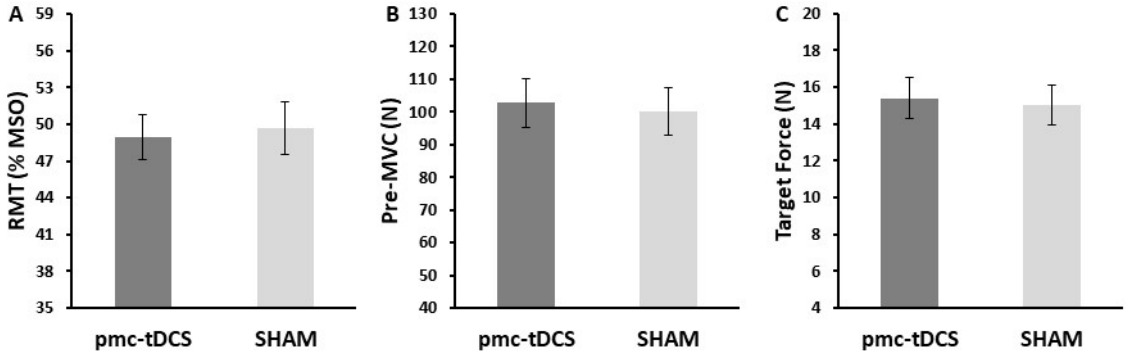


**Figure 2.** (A) RMT, (B) Pre-MVC, and (C) target force for the pmc-tDCS and SHAM conditions.

## TTF and Fatigue Index

Separated paired *t*-tests indicated that both the TTF ($P = 0.104$; d = 0.488; Figure 3A) and the fatigue index ($P = 0.985$; d = 0.005; Figure 3B) were not statistically different between the pmc-tDCS and SHAM conditions.

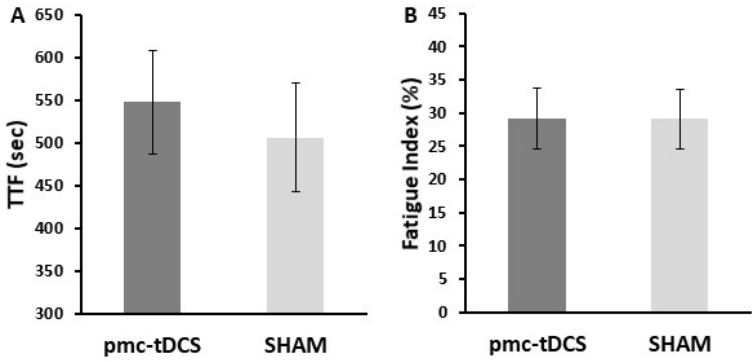


**Figure 3.** (A) TTF for the fatiguing contraction for the pmc-tDCS and SHAM conditions. (B) Fatigue index after the fatiguing contractions for the pmc-tDCS and SHAM conditions.

The *a*force and *a*EMG during the Fatiguing Contractions

The *condition* main effect ($P = 0.930$; $\eta_p^2 = 0.001$) and *condition* × *quartile* interaction ($P = 0.133$; $\eta_p^2 = 0.163$) were both non-significant for the *a*force. However, there was a quartile main effect ($P = 0.006$; $\eta_p^2 = 0.403$; (Figure 4A). Post-hoc analyses of the main effect indicated that none of the pairwise comparisons were significant, although a few of them just failed statistical significance ($P$ value range 0.05 – 1.00). For *a*EMG, the *condition* main effect ($P = 0.253$; $\eta_p^2 = 0.107$) and *condition* × *quartile* interaction ($P = 0.301$; $\eta_p^2 = 0.095$) were both non-significant. In contrast, the *quartile* main effect was significant ($P = 0.007$; $\eta_p^2 = 0.368$) as *a*EMG increased progressively throughout the fatiguing contractions (Figure 4B). Post hoc analysis of the *quartile* main effect revealed that the *a*EMG activity for quartile 4 was significantly greater than quartile 2 ($P = 0.028$), but all other pairwise comparisons were non-significant ($P$ value range = 0.068 – 1.00).

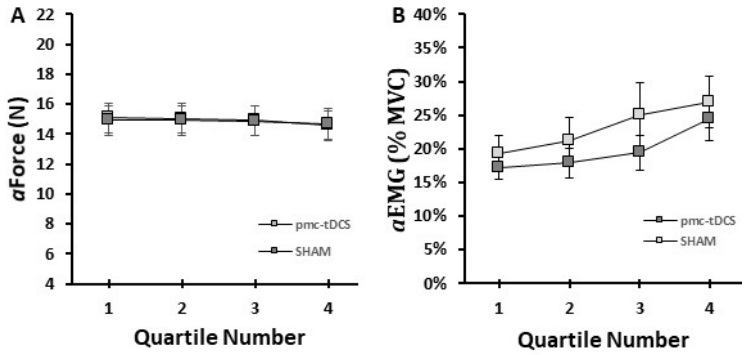


**Figure 4.** (A) *a*force and (B) *a*EMG for the pmc-tDCS and SHAM conditions across the four-time quartiles.

The Force Error and SD of Force during the Fatiguing Contraction

The *condition* main effect ($P = 0.532$; $\eta_p^2 = 0.033$) and the *condition* × *quartile* interaction ($P = 0.640$; $\eta_p^2 = 0.025$) were both non-statistically significant for the force error. However, there was a significant main effect for quartile ($P < 0.001$; $\eta_p^2 = 0.736$) as force error increased progressively throughout the fatiguing contractions (Figure 5A). Post hoc analysis of the *quartile* main effect revealed that the force error for quartile 4 was significantly greater than quartiles 1 ($P < 0.001$), 2 ($P < 0.001$), and 3 ($P = 0.006$). In addition, the force error was significantly greater for quartile 3 compared with quartiles 1 ($P = 0.004$) and 2 ($P < 0.001$). Finally, the force error was similar between quartiles 1 and 2 ($P = 0.344$). For SD of force, the *condition* main effect ($P = 0.792$; $\eta_p^2 = 0.006$) and the *condition* × *quartile* interaction ($P = 0.680$; $\eta_p^2 = 0.020$) were both non-statistically significant. However, there was a significant *quartile* main effect ($P < 0.001$; $\eta_p^2 = 0.616$) as SD of force increased progressively throughout the fatiguing contractions (Figure 5B). Post hoc analysis of the *quartile* main effect revealed that the SD of force for quartile 4 was significantly greater than quartiles 1 ($P = 0.002$), 2 ($P = 0.001$), and 3 ($P = 0.012$). In addition, the SD of force was significantly greater for quartile 3

compared with quartile 2 ($P < 0.001$). Finally, all other pairwise comparisons were non-significant ($P$ value range = 0.765 –1.00).

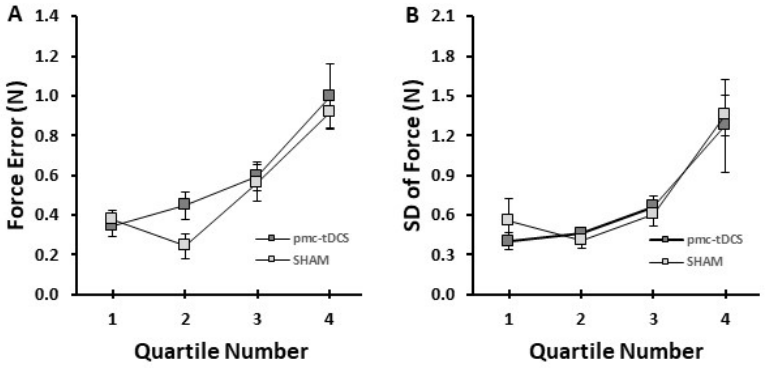


**Figure 5.** (A) Force error and (B) SD of force for the pmc-tDCS and SHAM conditions across the four-time quartiles.

9-HPT Times

For the 9-HPT times, the *condition* main effect ($P = 0.622$; $\eta_p^2 = 0.021$), *test* main effect ($P = 0.359$; $\eta_p^2 = 0.071$), and *condition* × *test* interaction ($P = 0.104$; $\eta_p^2 = 0.205$) were all non-statistically significant (Figure 6).

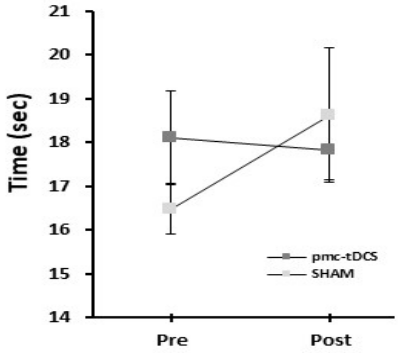


**Figure 6.** The 9-HTP times in the pre and post-tests for the pmc-tDCS and SHAM stimulation conditions.

# CHAPTER 4

# DISCUSSION

The primary purpose was to determine whether dual source pmc-tDCS delivered bilaterally could increase the TTF of a fatiguing contraction performed by hand muscles. The secondary purpose was to examine some of the neural mechanisms that may underlie any observed increases in TTF due to pmc-tDCS. The study produced three sets of main findings: 1) the TTF and fatigue index were not significant different between the pmc-tDCS and the SHAM conditions; 2) the FDI *a*EMG activity, force error, and SD of force all increased at statistically similar rates during the fatiguing contractions in the two stimulation conditions; and 3) the amount of transfer of motor skill from the precision grip task to the 9-HPT was also similar for the pmc-tDCS and SHAM stimulation conditions. Overall, the results suggest that dual source pmc-tDCS does not elicit meaningful reductions in the rate of increase of muscle fatigue development in a precision grip task.

## Influence of pmc-tDCS on TTF and the Fatigue Index

This was the first study to investigate the influence of pmc-tDCS on muscle fatigue in the most common experimental model of a submaximal isometric fatiguing contraction, which provides a high level of experimental control and ease of acquisition of well-described behavioral and physiological measurements during fatigue [1, 6, 27]. Although a trend was observed for the TTF to be greater in the pmc-tDCS condition compared with SHAM, this difference did not reach statistical significance. On the other hand, the fatigue index was almost identical for the two conditions following the fatiguing contraction. Thus, these results were contrary to the initial primary hypothesis. Importantly, these unexpected results could not have

been due to confounds due to the lack of differences in the any of the control measures taken before the fatiguing contraction such as RMT, but especially the Pre-MVC which determined the target force. Furthermore, the nearly identical values for the two stimulation conditions in the control measure of *a*force produced during the fatiguing contraction provided further evidence that the findings were not due to a random or systematic difference in experimental outcomes or procedures.

The negative findings for TTF and the fatigue index are not in agreement with the majority of prior tDCS studies that have targeted the DLPFC or M1 with unilateral tDCS using standard electrode montages [28, 29, 55]. The outcomes are also in contrast to the relatively few studies that have demonstrated both increased M1 excitability and motor skill acquisition of hand muscles as a result of unilateral premotor cortex tDCS application [56, 57]. Most importantly, the results are inconsistent with those of Anoushiravani et al. (2023), which detailed the original use of this electrode montage and provided most of the basis for the current study. Specifically, this study was comprehensive in that the sample comprised trained gymnasts who performed a number of complex motor tasks that collectively assessed a several motor abilities. The study also introduced an analogous dual source cerebellar electrode montage. Although both forms of stimulation were superior to SHAM the pmc-tDCS electrode montage induced somewhat greater effects compared to the cerebellar electrode montage. Since that found improvements in muscle activation, force production, muscle power, and motor coordination, it is difficult to reconcile the reasons for the contrasting findings of the current study. This is especially true considering those motor abilities would overlap somewhat with the ability to resist fatigue and the electrode montage and stimulation parameters were the same across studies.

However, the present results are congruent with a non-insignificant minority of studies that have not found any influence of tDCS on TTF of isometric contractions and other types of motor tasks [28, 29, 55]. Therefore, it cannot always be assumed that tDCS will elicit significant effects on muscle fatigue, despite the balance of the literature being weighted toward positive outcomes. This point is underscored by the results of Abdelmoula and colleagues who conducted two separate studies [58, 59] with the SO-M1 electrode montage utilizing submaximal isometric fatiguing contractions, albeit with different muscles across the two studies. One study found that tDCS failed to extend TTF or modulate any neural mechanisms of muscle fatigue when a thumb muscle performed the fatiguing contraction [59]. However, the main findings of the other study were that tDCS elicited a significant increase in TTF when the biceps muscle group performed the fatiguing contraction. Interestingly, this increase was not accompanied by any changes in M1 excitability [59]. This example of different findings in similar studies performed by the same experienced research group support the idea the interrelated conclusions of a recent [27]and several older reviews [28, 29, 55] that tDCS effects on TTF are variable, motor task dependent, subject to wide interindividual difference in response, and could be viewed as small to moderate even when they occur.

### Force and *a*EMG Measurements in the Fatiguing Contraction

Despite a relatively constant average force produced in the fatiguing contraction in both experimental conditions, there was a gradual rise in FDI *a*EMG activity, force error, and SD of force throughout the time course of the fatiguing contraction. These outcomes are not surprising as this basic pattern of results is a universal finding across all submaximal fatiguing contraction studies. The major mechanisms (decreased motor unit discharge rates, increased motor unit recruitment, increased group III and IV afferent feedback) of which have been meticulously

detailed in previous research over many decades [1, 3, 5, 6] as described in the Introduction. In the current study, it was hypothesized that the rate of rise in those aforementioned variables would be less in the pmc-tDCS condition compared with the SHAM condition, which would contribute to a shorter TTF in the SHAM condition relative to the pmc-tDCS condition. The results were also contrary to these predictions as *a*EMG activity, force error, and SD of force all increased over the four-time quartiles during the fatiguing contraction, but this increase was not statistically different between the pmc-tDCS and SHAM conditions. Based on theoretical considerations and the relevant existing tDCS fatigue literature, it was assumed that pmc-tDCS would increase premotor cortex excitability. This could increase M1 output due to the dense premotor cortex projections to M1 as suggested by [56], which would result in an extended TTF. In addition, the increased cortical excitability was also expected to acutely increase motor skill (decrease force error and SD of force) during the fatiguing contraction. This could be more energy efficient due to less deviations and corrections about the target force line and indirectly increase TTF in the pmc-tDCS condition through an acute enhancement of motor skill. However, not only was this not the case, but pmc-tDCS also failed to induce a transfer of motor skill learning as evidenced by the 9-HPT results. Finally, any hypothetical effects of pmc-tDCS on pain reduction were also likely not present based on the lack of differences in any of the behavioral variables between conditions, although no measures of exercise induced pain were undertaken in the present study. Taken together, the pattern of results in this study indicates that none of the originally proposed mechanisms of action of pmc-tDCS (increased M1 output, increased skill, decreased pain perception) are likely to have either been not present at all or so low in magnitude to have not induced any noticeable performance effects.

### Potential Explanations for the Lack of pmc-tDCS Effects on Muscle Fatigue

There are at least three possible explanations for the absence of significant effects of pmc-tDCS on any of the behavioral and physiological related fatigue outcomes. First, the submaximal isometric contraction task may not be the most appropriate model motor task to allow the realization of pmc-tDCS effects on muscle fatigue. A few reasons it was chosen for implementation in the current study was that it represented a logical starting point for investigation of the novel pmc-tDCS montage and the results would be comparable to many previous studies. However, it could be that pmc-tDCS would be more likely to influence more complex motor tasks as suggested by activation patterns in premotor cortex in complex tasks [56], the results of a prior premotor cortex unilateral tDCS motor skill study [56], and the previously described findings of Anoushiravani et al. (2023) [37]. Second, the choice of applying pmc-tDCS during the fatiguing contraction could have been problematic or at least suboptimal. Accordingly, many studies that have reported enhanced TTF when tDCS was applied immediately before or at rest between fatiguing contractions [28, 29, 55]. However, a roughly equal number of similar studies have found significant effects on muscle with concurrent stimulation protocols. Moreover, many of the most successful tDCS motor skill studies have involved simultaneous stimulation with the motor task [19, 20]. Third, only one stimulation session was conducted in the current study. A common criticism of tDCS motor skill studies that display negative findings is that repeated application over several successive days could have been needed to elucidate significant tDCS effects [19, 20, 24]. However, it appears that this idea has not been tested in tDCS fatigue studies in healthy individuals. Fourth, the study involved only healthy active young adults, which could have introduced ceiling effects [60-63] as suggested in previous skill studies, although many fatigue studies that demonstrated significant tDCS effects also comprised young adults.

## Limitations

The study had several limitations that should be briefly noted as these limitations are interrelated to the aforementioned factors for lack of significant pmc-tDCS effects. One limitation was that only variation of pmc-tDCS was included in the study. Another experimental condition(s) performed a week apart using some different combination of parameters could have yielded different results. For instance, it may have been more effective to apply pmc-tDCS for 20 minutes immediately before the fatiguing contraction commenced [29, 30, 64-66]. Lower or higher current strengths (e.g. 1 mA or 4 mA) [67, 68] or an electrode montage similar to premotor cortex motor skill studies could also have been utilized in a separate condition. Other related limitations that could have been addressed in this manner could have been the use of higher intensity intermittent contractions, which could have had a higher probability of being influenced by tDCS based on a series of tDCS strength training studies [69-74].

A final limitation is that the current study did not incorporate more sensitive physiological measurements that are superior or more sensitive than those used here such as TMS measures of voluntary activation paired with cervicomedullary MEPs recordings, and spinal reflex measurements to discriminate between cortical and spinal mechanism would have been ideal. However, given the complete absence of any behavioral or physiological differences between the pmc-tDCS and SHAM conditions, these measurements would almost certainly have not provided any novel information. Futures studies should systematically address these limitations so that a better understanding of the viability of the novel bilateral dual source pmc-tDCS montage can be determined.

## Conclusions

To summarize, there was no difference in TTF or the fatigue index between the pmc-tDCS and the SHAM condition. These primary outcome results were accompanied by lack of significant differences between the two conditions in the secondary outcome measures of the 9-HPT as well as the FDI *a*EMG, force error, and SD of force produced in the precision grip during the fatiguing contraction. This set of findings indicates that dual source pmc-tDCS does not attenuate the rate of fatigue development in the common fatigue experimental model involving a sustained submaximal isometric contraction, which was contrary to our original hypothesis and the only previous study using the pmc-tDCS electrode montage [37]. Therefore, future research is warranted and should continue to explore the influence of pmc-tDCS on different motor tasks that require movement accuracy, high force production, or the ability to resist fatigue. Finally, applying pmc-tDCS before motor task performance and over multiple days could be worthwhile aspects of alternative research designs in future studies.

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CURRICULUM VITAE

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**Education**

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| 2024 | M.S. Kinesiology<br>Department of Kinesiology<br>University of Nevada, Las Vegas<br>GPA: 4.00<br>Thesis: *The Influence of Dual Pre-Motor Cortex Transcranial Direct Current Stimulation on Muscle Fatigue*<br>Advisor: Brach Poston, Ph.D. |
| 2021 | B.S. Kinesiology<br>School of Integrated Health Sciences<br>University of Nevada Leas Vegas<br>GPA: 3.7 |
| 2021 | B.S. Nutrition<br>School of Integrated Health Sciences<br>University of Nevada Leas Vegas<br>GPA: 3.7 |
| 2015 | A.A Criminal justice<br>Community College of the Air Force |
| 2010 | A.A Liberal Arts<br>Lincoln College |

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**Professional Experience**

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| 2022-Present | Graduate Teaching Assistant<br>Department of Kinesiology and Nutrition Sciences<br>School of Integrated Health Sciences<br>University of Nevada, Las Vegas<br>Advisor: Sharon Jalene, Ph.D. |
| 2022-Present | Research Assistant<br>Neurophysiology of Movement Lab<br>Department of Kinesiology |

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| | University of Nevada, Las Vegas<br>Advisor: Brach Poston, Ph.D. |
| 4/2021- 2/2022 | Dietetic Internship<br>Sunrise hospital |
| 08/2019-05/2021 | UNLV Food Pantry Assistant Coordinator<br>University of Nevada, Las Vegas |
| 02/2018-08/2019 | Diet Technician<br>Desert Springs Hospital |
| 08/2010-10/2016 | Security Forces Patrolman<br>Tyndall Air Force Base, FL |