THE INFLUENCE OF BILATERAL DUAL SOURCE TRANSCRANIAL DIRECT CURRENT STIMULATION ON THE PROGRESSION OF MUSCLE FATIGUE

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ABSTRACT

Transcranial direct current stimulation (tDCS) applied unilaterally to the primary motor cortex (M1) can significantly prolong the time to task failure (TTF) of a fatiguing contraction. The primary purpose of the study was to examine the influence of bilateral dual source tDCS (ds-tDCS) applied over the left and right M1s (ds-tDCS) on the TTF of a precision grip task. This was accomplished through the utilization of a double-blind, randomized, SHAM-controlled, within-subjects design. Fourteen participants completed two experiments (ds-tDCS and SHAM stimulation conditions) with a seven-day washout period between sessions. Each experiment involved the performance of a sustained isometric fatiguing contraction using a precision grip (index finger and thumb) of the right hand while either ds-tDCS or SHAM stimulation was applied to the left and right M1 by two separate stimulation devices. Participants were directed to match a target force equivalent to 15% of the maximum voluntary contraction (MVC) force for as long as possible (TTF). The main findings were that both the TTF and the percentage decline in MVC force were not significantly different between the ds-tDCS and SHAM stimulation conditions. In addition, the force error, standard deviation (SD) of force, and EMG activity was not significantly different between the ds-tDCS and SHAM stimulation conditions. These findings suggest that ds-tDCS does not reduce the rate of progression of muscle fatigue in a sustained submaximal isometric contraction of hand muscles.

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CHAPTER 1: INTRODUCTION

Muscle fatigue is commonly defined as a transient decrease in the maximum force production capability of muscle due to exercise [1-6]. Muscle fatigue starts to develop within a few seconds after the start of exercise, progresses gradually, and influences all facets of human motor performance. Fatigue emerges during exercise due to both changes that occur at the muscle level (peripheral fatigue) and changes that occur in the central nervous system (central fatigue [1, 5, 7, 8]. The relative contribution of these two sites to the total fatiguability that manifests during physical activity depends on the details of the task such as the amount of muscle mass involved, the intensity of muscle contraction as a percentage of maximum, the muscles involved, the contraction type, and several others [4, 9, 10]. For example, it has been demonstrated that one half to two-thirds of the total fatiguability observed during submaximal sustained isometric contractions can be attributed to neural mechanisms occurring at the supraspinal level, whereas the number is surprisingly only about 25% for various types of sustained or intermittent MVC (maximum voluntary contraction) force tasks [5].

A multitude of interrelated alterations in neural processes typically transpire during the performance of sustained submaximal isometric fatiguing contractions. There is a progressive recruitment of additional motor units, which is primarily a reflection of enhancements in descending drive from the primary motor cortex (M1) to the motor neuron pool. This is in an effort to recruit new higher threshold motor units to compensate for declines in the discharge rates of some of the previously active motor units [1, 6, 11] and maintain the force required to continue the fatiguing contraction [1, 5, 6, 10]. The progressive increase in motor unit recruitment is accompanied by heightened overall EMG (electromyographic) activity and occasional bursts rates of EMG [12]. In addition, there are increases in effort perception, the

discharge rate variability of motor units, fluctuations in force, and force error [13]. Numerous changes in sensory feedback also occur during fatiguing contractions and contribute to fatigue development. For instance, the inhibitory input provided by group III and IV afferents to motor neurons and supraspinal sites [4, 5, 14] is enhanced during fatigue, whereas the excitatory input of group Ia afferents to motor neurons can decrease and further constrain overall muscle activation [10, 15].

Although numerous physiological adjustments during fatigue have been characterized, relatively few interventional methods have been developed to attenuate the accumulation of muscle fatigue. Established physical training methods incorporating training specificity (exercising in a fatigued state) and gradual progressive overload are the primary means of mitigating muscle fatigue along with various nutrition, supplement, and pharmacological approaches. However, these existing strategies are already widely recognized, may only apply to specific motor tasks or exercise environments, can be challenging to implement, and may be associated with adverse side-effects. Thus, novel modalities that could be combined with prevailing interventions could have significant implications in rehabilitation, sports, ergonomics, and motor disorders, given the widespread impact of fatigue on motor function [16, 17].

Non-invasive brain stimulation techniques have garnered increasing research attention over the past two decades as potentially safe, effective, and economical adjunct interventions for improving several different motor abilities [18-25]. Among these techniques, transcranial direct current stimulation (tDCS) has been the most extensively investigated and has shown the greatest potential for practical widespread application. The majority of tDCS studies have investigated its use for improving motor skill acquisition and learning. In these applications, movement accuracy improvements ranging between about 5 and 30% relative to SHAM stimulation have been

reported depending on the number of stimulation sessions, which is typically one [18, 23, 25, 26] although three-five sessions generally magnify the positive effects [18-20, 24]. The vast majority of these studies have used a unilateral electrode montage characterized by the anode being situated over M1 and the cathode over the contralateral supraorbital (SO) area (M1-SO montage). Moreover, this arrangement usually also enhances M1 excitability, which has been proposed to be at least one explanation for the simultaneous motor skill improvements. Furthermore, a noteworthy number of studies have also reported that tDCS applied via the SO-M1 electrode montage can also delay muscle fatigue and prolong TTF [27-32]. While these studies are less numerous compared to motor skill investigations, several review articles [28, 33] have reported that the weight of the available experimental findings indicate that tDCS applied unilaterally with a SO-M1 montage significantly extends the endurance time or TTF across a diverse number of motor tasks, albeit with effect sizes that range from small to moderate [28, 29, 33].

Despite the promising findings of many unilateral tDCS studies involving muscle fatigue, there is evidence that alternative electrode montages could yield even greater enhancements in motor performance. This would not be surprising as the standard unilateral SO-M1 montage could have a few drawbacks and represents just one of numerous potential effective tDCS electrode montages. For example, one variation termed the bihemispheric M1 montage involves the same arrangement as the SO-M1 montage with the exception that the cathode is placed over the contralateral M1 [34-36]. Although at least two competing theories exist in regard to the mechanisms of action of the bihemispheric montage, a systematic review and meta-analysis reported that the bihemispheric montages led to superior skill acquisition outcomes compared to unilateral tDCS montages [37]. Another recent novel innovation is dual source stimulation

(hereafter referred to as ds-tDCS) which involves the concurrent use of two independent tDCS devices to target two brain areas (e.g. left and right M1) at the same time. One variation of ds-tDCS not only significantly outperformed the SO-M1 montage, but also led to slightly greater motor skill improvements than the bihemispheric M1 montage [35]. More recently, both ds-tDCS given bilaterally to the two premotor cortices and to the two cerebellar hemispheres were able to increase maximum force and coordination in complex motor tasks performed by trained gymnasts [38]. Taken together, these findings imply that a ds-tDCS montage applied to the left and right M1s could potentially also reduce muscle fatigue to a greater degree compared to the SO-M1 montage used in prior studies.

The primary purpose of the study was to examine the influence of bilateral ds-tDCS applied over the left and right M1s (ds-tDCS) on the TTF of a precision grip task, whereas the secondary purpose was to identify physiological mechanisms that may mediate any ds-tDCS induced increases in TTF. This was achieved by directing participants to complete a sustained submaximal isometric fatiguing contraction in a ds-tDCS condition and a SHAM stimulation condition held on two different days with a one-week washout period. The fatiguing contractions were executed concurrent with either ds-tDCS condition or SHAM stimulation with recordings of EMG activity, force error, and standard deviation (SD) of force. The study had three interrelated hypotheses. First, ds-tDCS applied simultaneously to the two M1s would enhance the TTF and decrease the percentage change (decline) MVC force compared with SHAM stimulation. Second, the rates of increase in EMG activity, force error, and SD of force throughout the fatiguing contraction would be lower in the ds-tDCS condition compared with the SHAM stimulation condition. Third, the magnitude of motor skill transfer following the fatiguing contraction would be greater in ds-tDCS condition compared with the SHAM

stimulation condition. Collectively, the hypotheses were not only based on prior unilateral tDCS studies involving motor skill and fatigue, but also bihemispheric [34-37] and ds-tDCS motor performance investigations [35, 38].

CHAPTER 2: METHODS

Participants

Fourteen healthy adults (6 males, 8 females; average age: 28.0 ± 7.5 years) volunteered to participate in the study. All participants were right-handed as indicated by the Edinburgh Handedness Inventory [39] (average laterality quotient: 0.94 ± 0.1). Participants provided written informed consent before participating in the study. Participants were excluded if they were left-handed, had any neurological disorders, psychiatric conditions, history of migraines, history of seizures, or uncontrolled medical conditions. Furthermore, participants were screened to ensure that they did not meet the exclusion criteria for tDCS or transcranial magnetic stimulation (TMS) studies [40, 41]. The protocol of the study was approved by the Institutional Review Board at the University of Nevada, Las Vegas and all of the procedures were performed in accordance with the standards of the Declaration of Helsinki.

Experimental Design

A double-blind, randomized, SHAM-controlled, within-subjects experimental design was used for this study. Although between-subjects designs were utilized in the majority of early tDCS studies, an increasing number of more recent studies are using within-subjects designs. This is likely due to accumulating evidence that there are substantial interindividual variations in genetic, anatomical, and physiological characteristics [42, 43] that can influence the ability of tDCS to induce increases in motor performance. Accordingly, the within-subjects design was used to preclude differences in these factors from influencing the results and to provide higher statistical power compared with between-subjects designs [44].

Experimental Protocol and Procedures

Each participant completed two testing sessions that were held on separate days with a seven-day washout between the two sessions, which is the most typical washout time period employed in tDCS studies [13, 45]. Participants received either ds-tDCS or SHAM stimulation with the experimental condition being randomized using a commonly used online tool (Research Randomizer; www.randomizer.org). An equal number of participants performed the ds-tDCS condition first and the SHAM condition second and vice versa. In each experiment, participants completed the following seven experimental steps in succession: 1) 10 trials of a 9-hole peg test (pre-9-HPT); 2) the motor "hotspots" of the left and right first dorsal interosseus (FDI) muscles were located and marked over the scalp areas corresponding to the right and left M1 using TMS; 3) resting motor threshold (RMT) was also obtained using TMS, but only for the left M1 (right FDI); 4) three pre-MVCs; 5) ds-tDCS or SHAM stimulation was applied for three minutes before and for up to 17 minutes during the fatiguing contraction; 6) three post-MVCs; and 7) post-9-HPT (10 trials). Accordingly, the two experimental sessions were identical except for the stimulation condition performed. A schematic of the study protocol and experimental procedures is depicted below in Figure 1.

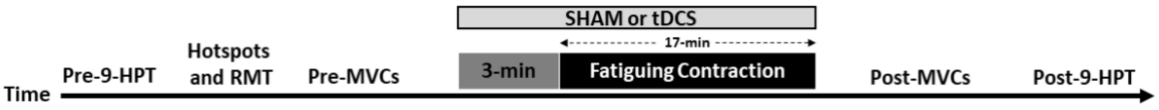

Figure 1. Experimental protocol. Schematic diagram of the protocol of the study and experimental procedures. All participants were required to complete a ds-tDCS session and a SHAM stimulation session in counterbalanced order. The main part of the experiment involved a sustained submaximal isometric fatiguing contraction that was executed during application of either ds-tDCS or SHAM stimulation. The fatiguing contraction was preceded by pre-9-HPT, TMS, and pre-MVC testing and followed by post-MVC and post-9-HPT testing.

9-HPT. The Rolyan 9-HPT was conducted at the start and end of each experiment with 10 trials being completed at each of the two timepoints. The 9-HPT is a common, well-accepted

upper limb manual dexterity test [46] and is one of the tests incorporated into the motor battery of the NIH toolbox [47]. All 9-HPT trials were executed with the right hand and arm and timed according to standard procedures [46]. Participants reached into the pegboard dish and grasped each of the 9 pegs using a precision grip using of the index finger and thumb, placed the pegs into the 9 holes on the other side of the pegboard dish, and returned the pegs to the dish. This sequence of events constituted one trial and participants were directed to execute each trial as fast and as accurately as possible.

The 9-HPT served two interrelated purposes in the study: 1) to assess motor skill transfer from the isometric precision grip task performed during the fatiguing contraction to the hand and arm movement of the 9-HPT that involved a precision grip when retrieving the pegs; and 2) to provide a complementary measure of motor accuracy under fatigued conditions (after cessation of the fatiguing contraction) to the measure of force error that was collected throughout the fatiguing contraction (see below). Thus, if TTF was longer in the ds-tDCS condition and force error was concomitantly reduced compared to SHAM, this would represent additional support for the idea that that any observed TTF increases under ds-tDCS were at least partly attributable to enhanced motor skill under fatigue.

Motor Hotspot, RMT, and EMG measurement. A Magstim 200^2 equipped with a double 70 mm remote control figure-of-eight coil was used to locate the motor "hotspots" of the left and right FDIs and quantify RMT (right FDI only) according to standard methodological procedures [48]. In brief, surface EMG electrodes were placed the right and left FDI muscles of each hand using a belly tendon montage. Motor evoked potentials (MEPs) were elicited by single TMS pulses in the left followed by the right FDI. The TMS coil was oriented tangential to the scalp in a manner in which the handle was directed backwards and laterally at an angle of 45 degrees

relative to the midline. TMS pulses were applied until the sites on the scalp over two M1s that elicited greatest MEPs in each of the FDI muscles was located. These two spots were marked for subsequent placement of tDCS electrodes (both M1s) and RMT assessment (left M1 only). The RMT was measured because it is a basic measure of M1 excitability and individuals with lower RMTs may respond better to tDCS [49, 50]. Thus, a lower RMT could potentially correlate with longer TTF in the ds-tDCS condition.

MVC Task. All participants were seated comfortably in an upright position facing a computer monitor that was located 1 meter away at eye level. The upper body joint angles (shoulder abducted to 45°, elbow flexed to 90°) and positioning (wrist neutral, hand semi-supinated) was similar to previous studies involving the precision grip and this experimental arrangement. The force applied by the right index finger and thumb in a precision grip were measured by two one-dimensional force transducers (model S215; Strain Measurement Devices; Meriden, Connecticut) located on the left and right side of a grip manipulandum mounted on a table. The total force exerted by the index finger and thumb was presented as a red trace on the computer screen. Participants were instructed to produce the maximum force possible in the shortest possible time and to hold this maximum for approximately five seconds [51, 52]. Three pre-MVC trials and three post-MVC trials were recorded and one minute of rest was enforced between all MVC trials. The pre-MVC trial with the highest force was termed the pre-MVC and served as the reference to calculate the fatiguing contraction target force (15% of MVC). The first post-MVC was used to quantify fatigue as a percent decline in MVC pre- to post-fatiguing contraction. This MVC was undertaken as quickly as possible (usually 10-20 seconds) after the fatiguing contraction ended.

Ds-tDCS Application. Two separate NeuroConn DC Stimulators were used to apply ds-tDCS to the left and right M1. The current strength delivered by each of the two simulators was set to 1 mA. The ds-tDCS electrode montage was similar to Naros et al. (2016) [33] and therefore involved two separate SO-M1 montages. Specifically, the each of the cathodes were placed over the eyebrows and the anodes were placed over the corresponding contralateral M1s hotspots. The cathodes comprised two rubber electrodes (5 × 7 cm), whereas the dimensions of the anodes were 5 × 5 cm, which are similar electrode sizes as used in two different bilateral M1 montages by Naros et al. (2016) [33]. All four electrodes were housed in saline-soaked sponges according to the most common practice, as opposed to using a gel and placing the electrodes directly on the scalp or skin of the forehead. Finally, two rubber straps were used to hold the two sets of two electrodes in place.

The total stimulation time was set to a total of 20 minutes as mentioned above. The details of the stimulation timing relative to the fatiguing contraction are depicted in Figure 1. Briefly, the stimulator was first allowed to run for 3 minutes immediately prior to the start of the fatiguing contraction [43]. Consequently, the fatiguing contraction started and the stimulator was allowed to operate for up to 17 minutes, although no participants were able to hold the fatiguing contraction for the full 17 minutes. Accordingly, the duration of stimulation was somewhat different across participants based on their individual TTF achieved, which is similar to studies by another research group [31, 32]. When each participant reached their individual TTF, the stimulators were immediately turned off by one of the investigators while the post-MVC task was being prepared. In line with our prior studies, the delivery of ds-tDCS or SHAM stimulation through programming of the two tDCS devices was done by a research team member who was

not involved in the data collection aspect of the experiments [13, 53, 54]. Similarly, investigators who were involved in the data collection were blinded to the experimental condition.

Fatiguing Contraction. The precision grip task used for the fatiguing contraction was identical to that used in prior motor learning [52, 53] studies and a previous fatigue study [13]. Thus, the fatiguing contraction also used a comparable setup and precision grip task as the MVC assessment, except that it involved submaximal force production. Participants sustained the fatiguing contraction in a constant posture for as long as possible until task failure. The target force was set to 15% of the pre-MVC value and displayed on a monitor. More specifically, a template was displayed on computer monitor in front of the participant that indicated a black horizontal target force line. Participants were directed to match their precision grip force (red trace) produced by the thumb and index finger (total force) to the horizontal target force line as accurately as possible. A second horizontal black line corresponding to 90% of the target force was placed below the target force line as a demarcation point to avoid allowing the force to fall below. Real-time force feedback was displayed as a red line and participants directed to match that line to the target force line as accurately as possible throughout the fatiguing contraction. The total time that the target force could be sustained within the constraints of the task was quantified as the TTF of the fatiguing contraction. Termination criteria were the same as previous studies [12, 13] and included: 1) force dropping below the 90% threshold for >3 continuous seconds; 2) inability to maintain the required hand, arm, or body posture despite verbal warnings; and 3) volitional discontinuation of the contraction with an abrupt force decline, which is the most common reason for task termination in isometric fatiguing contractions [13].

Data Analysis

Data in all experiments were collected using a custom-written script in the Signal programming (CED, Cambridge UK), whereas the offline data analyses were performed with a custom-written Python programming language script (Fredericksburg, Virginia, USA) and Signal scripts. The primary dependent variables were the TTF and the percentage decline in MVC force (pre to post-MVC). The secondary dependent variables included: RMT, Pre-MVC force, target force, average force, average EMG, force error, and SD of force. The RMT, Pre-MVC force, target force, and average force were considered to be control variables as systematic differences in these values between conditions could confound the results. The average force, average EMG, force error, and SD of force were recorded during the entirety of the fatiguing contractions and were quantified in four different epochs (E1, E2, E3, and E4) at 25% demarcation points over the fatiguing contraction.

The RMT was defined as the lowest stimulus intensity as a percentage of maximal stimulator output (% MSO) that produced MEP amplitudes ≥ 50 μV in at least 5 out of 10 successive trials in the right FDI. The Pre-MVC was denoted as the highest MVC of the pre-MVCs and the target force was calculated as 15% of this value in all experimental sessions. TTF was calculated as the time that the fatiguing contraction could be maintained until one of the criteria of task termination criteria occurred. Accordingly, the percentage difference between the Pre-MVC and the post-MVC performed after the fatiguing contraction was taken as the fatigue index and referred to as the percentage decline in MVC [1]. During the fatiguing contraction, the average force, average EMG, force error, and SD of force were obtained and analyzed over the four epochs and calculated as follows: 1) average force was simply computed as the mean force produced; 2) the interference EMG processing involved removing the DC bias, full-wave rectification, and normalizing the values to the maximal rectified EMG obtained in the Pre-MVC

trials; 3) the force error was quantified by calculating the difference between the target force line and the actual force produced at each sampling point. Next, the absolute value of these differences was taken and averaged [13, 52, 53]; and 4) the SD of force was simply determined as the SD of the force produced over each epoch.

Statistical Analysis

The TTF, percentage decline in MVC, RMT, Pre-MVC, and target force were compared between the ds-tDCS and SHAM conditions with separate two-tailed paired *t*-tests. The average force, average EMG, force error, and SD of force were compared between the ds-tDCS and SHAM conditions and epochs with separate 2 *condition* (ds-tDCS, SHAM) x 4 *epoch* (E1, E2, E3, E4) within-subjects ANOVAs. In contrast, the 9-HPT was analyzed with a 2 *condition* (ds-tDCS, SHAM) x 2 *test* (pre, post) within-subjects ANOVA. The significance level was set was set to $P < 0.05$ for all statistical tests. Data are depicted as the means +/- the standard errors in all of the figures. Lastly, effect sizes are reported as Cohen's *d* (*t*-tests) and partial eta squared values (ANOVAs).

CHAPTER 3: RESULTS

RMT, Pre-MVC, and Target Force

Paired *t*-tests revealed that there were no statistically significant differences between the ds-tDCS and SHAM conditions for RMT ($P = 0.449$, $d = 0.208$, Figure 2A), pre-MVC ($P = 0.756$, $d = 0.085$, Figure 2B), or target force ($P = 0.756$, $d = 0.085$, Figure 2C).

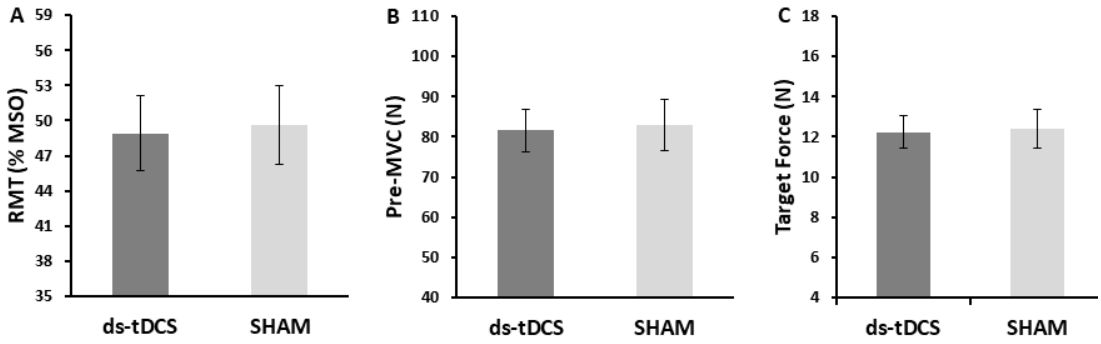

Figure 2. RMT (A), Pre-MVC (B), and target force (C) in the ds-tDCS and SHAM conditions.

TTF and Percentage Decline in MVC Force

Paired *t*-tests revealed no statistically significant differences between the ds-tDCS and SHAM conditions for the TTF ($P = 0.570$; $d = 0.156$; Figure 3A) or the percentage decline in MVC force ($P = 0.456$; $d = 0.205$; Figure 3B).

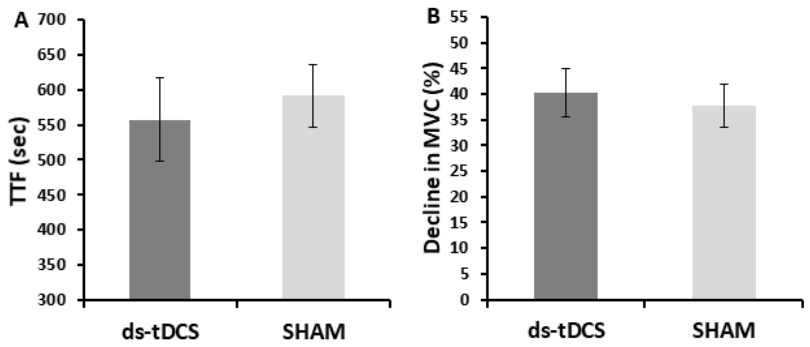

Figure 3. TTF (A) and decline in MVC force (B) in the ds-tDCS and SHAM conditions.

Average Force and Average EMG

For average force, the main effect for *condition* ($P = 0.668$; $\eta_p^2 = 0.015$), main effect for *epoch* ($P = 0.071$; $\eta_p^2 = 0.208$), and the *condition* × *epoch* interaction ($P = 0.774$; $\eta_p^2 = 0.011$) were all not statistically significant (Figure 4A-B). For average EMG, both the main effect for *condition* ($P = 0.998$; $\eta_p^2 = 0.000$) and *condition* × *epoch* interaction ($P = 0.628$; $\eta_p^2 = 0.043$) were not statistically significant. However, there was a significant main effect for *epoch* ($P = 0.021$; $\eta_p^2 = 0.270$) due to a progressive increase in EMG activity over the course of the fatiguing contractions (Figure 4C-D). Post hoc analysis of the *epoch* main effect indicated that the average EMG activity for epoch 4 was significantly greater compared with epoch 1 ($P = 0.013$), but all other pairwise comparisons were not significant (P value range = 0.065–1.00).

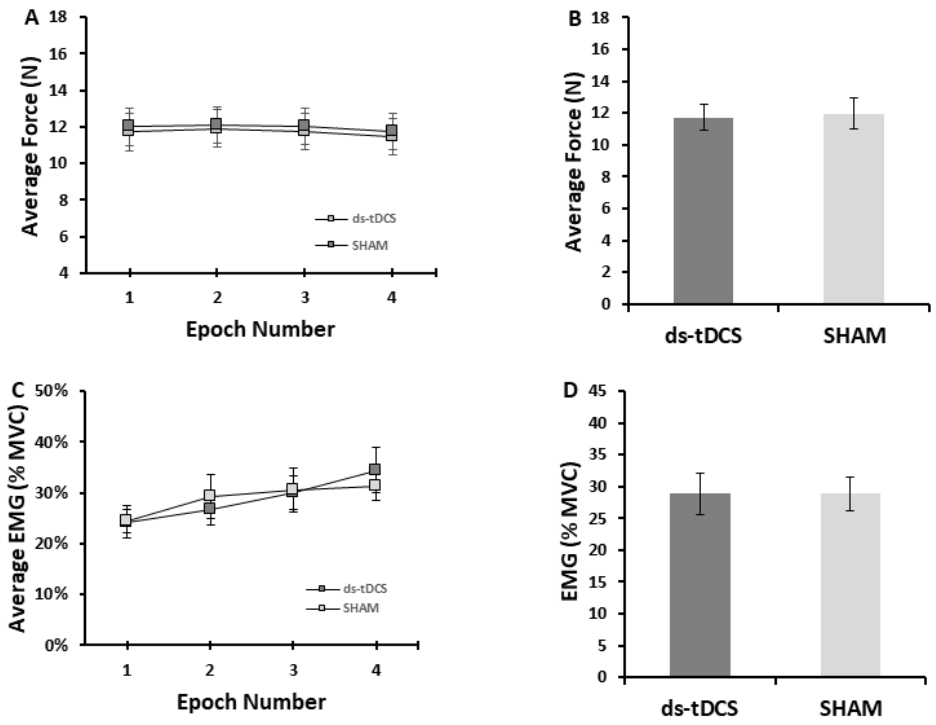

Figure 4. Average force and average EMG in the ds-tDCS and SHAM conditions (A), average force produced in the ds-tDCS and SHAM conditions when data were collapsed across the fours epoch is shown for illustration (B), average EMG activity in the four epochs for the ds-tDCS and SHAM stimulation conditions (C), average EMG activity for the ds-tDCS and SHAM conditions when data were collapsed across four epochs is shown for illustration (D).

Force Error and SD of Force

For force error, both the main effect for *condition* ($P = 0.413$; $\eta_p^2 = 0.052$) and *condition* × *epoch* interaction ($P = 0.796$; $\eta_p^2 = 0.01$) were not statistically significant. However, there was a significant main effect for epoch ($P = 0.028$; $\eta_p^2 = 0.279$) due to a progressive increase in force error over the course of the fatiguing contractions (Figure 5A-B). Post hoc analysis of the *epoch* main effect indicated that the force error for epoch 3 and epoch 4 were significantly greater compared with epoch 2 ($P = 0.001$ and $P < 0.001$, respectively). In addition, the force error was significantly greater for epoch 4 compared with epoch 3 ($P = 0.024$). All other pairwise comparisons were not significant (P value range = 0.607–1.00).

For SD of force, the main effect for *condition* ($P = 0.356$; $\eta_p^2 = 0.066$), main effect for *epoch* ($P = 0.088$; $\eta_p^2 = 0.181$), and the *condition* × *epoch* interaction ($P = 0.786$; $\eta_p^2 = 0.009$) were all not statistically significant (Figure 5C-D).

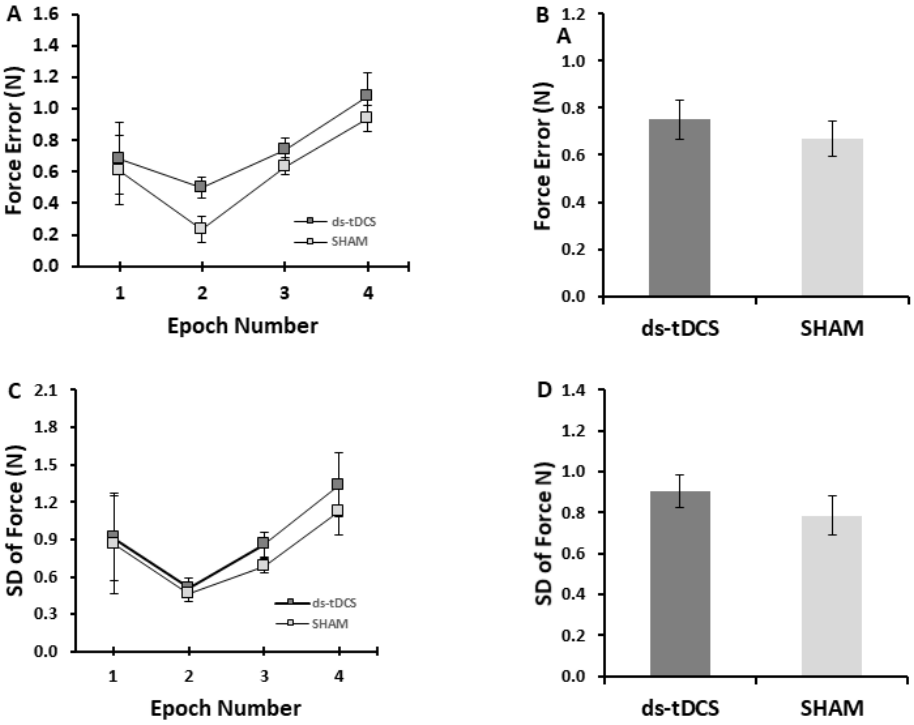

Figure 5. Force error and SD of force in the ds-tDCS and SHAM conditions (A), force error in the ds-tDCS and SHAM conditions when data were collapsed across the fours epoch is shown for illustration (B), SD of force in the four epochs for the ds-tDCS and SHAM stimulation conditions (C), SD of force for the ds-tDCS and SHAM conditions when data were collapsed across four epochs is shown for illustration (D).

For the 9-HPT, the both main effect for condition ($P = 0.351$; $\eta_p^2 = 0.067$) and the *condition* × *test* interaction ($P = 0.156$; $\eta_p^2 = 0.149$) were not statistically significant. However, there was a significant main effect for *test* ($P = 0.025$; $\eta_p^2 = 0.331$; Figure 6), which indicated that the 9-HPT times were significantly lower in the pre-test compared with the post-test.

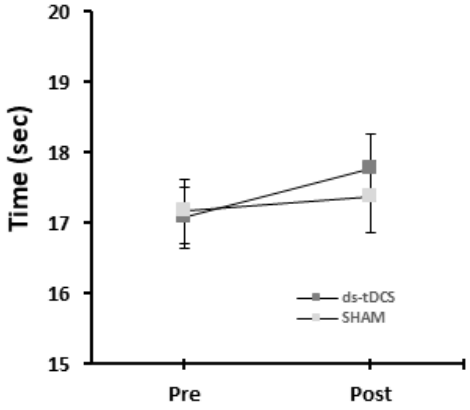

Figure 6. Pre- and post-peg times in the ds-tDCS and SHAM conditions.

CHAPTER 4: DISCUSSION

The primary purpose of the study was to examine the influence of bilateral dual source tDCS (ds-tDCS) applied over the left and right M1s on the TTF of a precision grip task, whereas the secondary purpose was to identify physiological mechanisms that may mediate any ds-tDCS induced increases in TTF. The study yielded three main findings. First, there were no statistically significant differences for either the TTF or the percentage decline in MVC between the ds-tDCS and the SHAM stimulation conditions. Second, the rates of increase in EMG activity, force error, and SD of force during the fatiguing contractions were comparable for the ds-tDCS and SHAM stimulation conditions. Third, motor skill transfer assessed under fatigue did not differ between the ds-tDCS and SHAM stimulation conditions. Collectively, these findings suggest that ds-tDCS applied concurrently to the left and right M1s does not reduce the rate of progression of muscle fatigue in a sustained submaximal isometric contraction of hand muscles.

TTF of the Fatiguing Contraction and Percentage Decline in MVC

To our knowledge, this was the first study to investigate the influence of ds-tDCS on muscle fatigue. Although many possible motor tasks have been used to investigate the phenomenon of muscle fatigue, the current study employed a submaximal isometric fatiguing contraction sustained at a relatively low target force performed unilateral by muscles of the hand. This was set of task details was selected because it is the most common in the literature as it allows for the most rigorous experimental control and more easily allows concomitant measurements of the physiological adjustments that accompany the progression of fatigue [1, 6, 27]. Most importantly, up to 66% the total fatigue development in this experimental paradigm is due to mechanisms emanating from cortical areas [5], which should have allowed the highest probability in detecting any positive effects of ds-tDCS application.

It was originally hypothesized that ds-tDCS applied concurrently to the left and right M1s would enhance TTF and reduce the decline in MVC force observed immediately after the fatiguing contraction when compared to SHAM stimulation. Contrary to these expectations, the TTF and percentage decline in MVC force was nearly identical between the ds-tDCS and SHAM stimulation conditions. Therefore, ds-tDCS neither attenuated the rate of development of fatigue in the fatiguing contraction nor the amount of fatigue quantified shortly following task failure. Since the control measures of Pre-MVC, target force, and RMT obtained before the fatiguing contraction as well as the average force produced during the fatiguing contraction were not different between stimulation conditions, the failure of ds-tDCS to influence the manifestation of fatigue could not be a consequence of potential confounding factors. In summary, the similar values obtained for all control measures between the two conditions strongly implies that experimental model and research design should have allowed the identification of significant differences in the primary outcome measures of TTF and percentage decline in MVC if they would have been present.

The present findings are in contrast to the prevailing results within the extant literature regarding the impact of tDCS on muscle fatigue and TTF. It is noteworthy that these prior investigations have encompassed a diverse array of motor tasks, muscle groups, stimulation parameters, and electrode montages including the stimulation of lower limb muscles [27-29, 55, 56], which are thought to be less susceptible to tDCS compared with hand muscles. However, a substantial proportion of these studies employed analogous experimental paradigms (submaximal isometric contractions) to that utilized in the current study [28, 30-33], but no studies to date have used a ds-tDCS for the mitigation of muscle fatigue. Moreover, the current findings also appear to be at odds with tDCS motor skill studies that have utilized the SO-M1

montage [18-20, 23, 24, 36], a bihemispheric montage [34-36], and various types of ds-tDCS applied to several brain regions [35, 38]. In contrast, the findings corroborate the observations of Abdelmoula and colleagues who reported that tDCS did not influence the TTF or fatigue-related changes in neural adjustments when a thumb muscle sustained a submaximal isometric contraction [57]. Interestingly, this same research group found a significant enhancement of TTF in a submaximal isometric contraction task involving the elbow flexors due to M1 tDCS, despite no changes in MEP amplitudes (cortical excitability) [57]. These conflicting findings underscore the fact that a non-trivial minority of tDCS motor skill [18] and fatigue studies [28, 29, 33] have failed to detect performance. Of paramount importance is the fact that even when tDCS has been shown to improve muscle fatigue resistance, the overall effects have been modest according to reviews and meta-analyses [28, 29, 33]. These lines of reasoning suggest that various forms of tDCS may not invariably elicit significant enhancements in motor performance, particularly with respect to muscle fatigue. In addition, tDCS effects could also be construed as variable, less efficacious than initially postulated [27], and highly contingent upon individual susceptibility to brain stimulation [42, 43]. Overall, the data presented here provide evidence that ds-tDCS application may not constitute an effective adjunct modality for attenuating muscle fatigue development, notwithstanding possible physiological advantages it may confer [27].

EMG and Force Changes in the Fatiguing Contractions

During sustained submaximal isometric fatiguing contractions, where the target force level is maintained for the maximum possible duration, a consistent observation is the progressive increase in surface electromyography (EMG) amplitude of the involved musculature [1, 3, 6]. This phenomenon is attributed to the recruitment of additional motor units to maintain the required force output [5] and a concomitant decrease in the conduction velocity of muscle

fiber action potentials [17]. Concurrently, there is a marked increase in force error and the SD of force during the fatiguing contractions [2, 3, 8, 13]. These alterations in motor output primarily stem from the aforementioned progressive and occasionally transient recruitment [12] of higher threshold motor units, which innervate a greater number of muscle fibers compared to the first recruited smaller motor units, resulting in more pronounced deviations relative to the target force line.

One of original hypotheses posited that the rate of increase in EMG activity, force error, and SD of force during the fatiguing contraction would be attenuated in the ds-tDCS condition compared to SHAM. This was predicated on previous findings that tDCS may simultaneously and acutely augment M1 output (cortical excitability), improve motor skill (greater contraction efficiency with less energy expense), and possible reduce pain perception. Furthermore, based on the existing bihemispheric and ds-tDCS literature, these effects were anticipated to be greater compared with studies who had found obtained such effects with the SO-M1 montage [35, 37, 38], possibly through better hemispheric cooperation [36]. The average EMG activity, force error, and SD of force all demonstrated a progressive increase throughout the fatiguing contractions. However, the rates of increase were remarkably similar and not statistically different between the ds-tDCS and SHAM conditions. This set of findings indicates the none of aforementioned proposed mechanisms of action of ds-tDCS were likely to have occurred. Specifically, even the most probably mechanism of enhanced cortical excitability, which could underlie both increases in M1 output and motor skill likely did not manifest. Although M1 excitability was not directly measured during and after the fatiguing contraction by direct physiological measures of MEPs, cervicomedullary MEPs, Hoffman reflexes, and M-waves, the more indirect measures of EMG, force error, and force rise clearly pointed to a lack of enhanced

cortical excitability to counteract fatigue in the ds-tDCS condition. Furthermore, the similar force error, SD of force, and 9-HPT times (transfer of skill) recorded during and after the fatiguing contraction provided more indirect evidence that increased cortical excitability was not present as indicated by the absence of any improvements is force accuracy or variability. Collectively, the findings provided no evidence for any effects of ds-tDCS on basic behavioral or physiological measurements taken during or after fatiguing contractions.

Potential Factors Responsible for the Failure of ds-tDCS to Delay Fatigue Progression

The failure of ds-tDCS to impact muscle fatigue development was unanticipated based on the current available related literature. A number of potential factors could have contributed to these results, but are speculative in nature given the findings and the physiological recordings employed. Briefly, the most likely reasons for the negative findings could include: 1) the combination of ds-tDCS parameters such as stimulation timing, duration, current strength, and finer details of the electrode montage may not have been optimal for the application of addressing fatigue resistance; 2) it is possible that multiple consecutive days of stimulation [19, 20, 24] combined with intense training under fatigue could be needed to elicit meaningful effects, although this approach has not been attempted in fatigue studies to our knowledge; and 3) ds-tDCS may not be able to produce noticeable effects in young, healthy, physically active adults like those who constituted the current study due to ceiling effects [58-61].

Study Limitations

The study had various limitations that warrant consideration when interpreting the findings relative to the existing literature on tDCS and muscle fatigue. Perhaps the greatest limitation was the timing of stimulation relative to task performance. This was the most difficult decision involved in the experimental design as previous studies have shown that applying tDCS

before [29, 30, 55, 56, 62] and during the fatiguing contraction [31, 32] have been effective. Ultimately, it was decided to apply the stimulation during the task based on the balance of both tDCS motor skill [18-20, 23-25] and fatigue studies [31, 32]. Nevertheless, application of ds-tDCS before the fatiguing contraction could very well be more efficacious and could be further addressed in subsequent studies. The 1 mA current strength utilized could be viewed as another limitation of the study. While this has been the most typically used current strength and has been effective in numerous motor skill and fatigue studies, this does not preclude the possibility that greater current levels could led to greater enhancements in M1 output to spinal motor neurons and therefore be more useful appropriate for increasing resistance to fatigue. Accordingly, current strengths of up to 4 mA have been undertaken in a several fatigue studies [63-65]. In addition, the combination of task details in the study involving a sustained isometric contraction using primarily the small muscles of the hand and forearm at a rather low contraction intensity (15%) relative to maximum may not have been ideal for detecting ds-tDCS effects on muscle fatigue. Accordingly, a number of strength training studies [66-71] conducted at much higher training intensities have found that tDCS can significantly increase the workload of training sessions. Similarly, tDCS has also enhanced force production during maximal isometric contractions in healthy adults [72]. Therefore, intermittent fatiguing contractions or sustained MVC experimental protocols could be more sensitive paradigms and make it more likely for ds-tDCS to exert effects on muscle fatigue. These types of experimental models would also have more ecological validity, but have the disadvantages of being more difficult to control, conduct simultaneous physiological measurements, and having a greater reliance on peripheral fatigue mechanisms compared to submaximal isometric contraction experimental arrangements [27]. Finally, the study could have benefitted from better, more direct physiological recordings such as

measures of cortical voluntary activation using TMS, cervicomedullary MEPs, and spinal reflex assessments. However, it is very improbable that any of these measures would have differed across the ds-tDCS and SHAM conditions given the results of the more basic physiological measurements. In conclusion, futures studies that explore the effects of tDCS on fatigue should apply it at different time points relative to the fatiguing task, use greater stimulation intensities, and perhaps focus on intermittent high-intensity muscle contractions.

Conclusions

Ds-tDCS applied to the left and right M1s simultaneously and during performance of a fatiguing contraction involving a precision grip task did not significantly prolong the TTF of a fatiguing contraction or affect the magnitude of reduction of MVC force after the fatiguing contraction ceased. In addition, the rates of increase in average EMG, force error, and SD of force were nearly identical between the ds-tDCS and SHAM stimulation conditions performed on different days. There was also no evidence of a transfer of motor skill in the presences of fatigue due to ds-tDCS. The findings indicate that ds-tDCS does not mitigate the progression of fatigue, at least within the experimental paradigm of the present study. Additional research will be needed to determine the viability of different bihemispheric or ds-tDCS electrode montages for the mitigation of muscle fatigue. Relatedly, alternative stimulation regimes and parameters such as repeated daily stimulation and the targeting of other brain areas could be investigated. This will be challenging due to the number of possible combinations of stimulation parameters possible based on the studies in the literature that have reported significant tDCS effects on either motor skill or muscle fatigue in numerous populations.

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70. Rodrigues, G. M., A. Paixao, T. Arruda, B. R. R. de Oliveira, G. A. Maranhao Neto, S. R. Marques Neto, E. Lattari, and S. Machado. "Anodal Transcranial Direct Current Stimulation Increases Muscular Strength and Reduces Pain Perception in Women with Patellofemoral Pain." *J Strength Cond Res* 36, no. 2 (2022): 371-78.

71. Vieira, L. A. F., E. Lattari, M. A. de Jesus Abreu, G. M. Rodrigues, B. Viana, S. Machado, B. R. R. Oliveira, and G. A. Maranhao Neto. "Transcranial Direct Current Stimulation (Tdcs) Improves Back-Squat Performance in Intermediate Resistance-Training Men." *Res Q Exerc Sport* 93, no. 1 (2022): 210-18.

72. Tanaka, S., T. Hanakawa, M. Honda, and K. Watanabe. "Enhancement of Pinch Force in the Lower Leg by Anodal Transcranial Direct Current Stimulation." *Exp Brain Res* 196, no. 3 (2009): 459-65.

CURRICULUM VITAE

Eliza Clinton

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Las Vegas, NV 89154
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EDUCATION

Aug. 2023-Present	Therapeutic Recreation Certificate Program, SUNY Cortland
Aug. 2022-Present	M.S. Kinesiology, University of Nevada, Las Vegas (UNLV)
Aug.2017-Dec. 2021	B.S. Kinesiology, University of Nevada, Las Vegas (UNLV) Minor: Neuroscience

PRESENTATIONS/PUBLICATIONS

De Guzman KA, Young RJ, Contini V, Clinton E, Hitchcock A, Riley ZA, & Poston B. The Influence of Transcranial Alternating Current Stimulation on Fatigue Resistance. Brain Sciences. 2023; 13(8):1225.

Clinton, Eliza M. & Moctezuma, Mirna. Pushing Psychedelic Drugs as a Modern Mental Illness Treatment. 2017, November.

Instructor: Nicole Espinoza, SCI 101 Presentation

EXPERIENCE

Aug. 2022-Present Graduate Assistant, Neurophysiology of Movement Lab at UNLV
I execute experiments under the guidance of the Principal Investigator (PI), abide by experimental guidelines, explain experimental procedures to participants, and demonstrate proper and safe usage of equipment.

Aug. 2022-Present Graduate Teaching Assistant, Human Anatomy and Physiology I & II
I assist with instructing laboratory sections of Anatomy and Physiology I and II. My primary duties include providing resources to optimize learning, assisting students when completing assignments, demonstrating safe laboratory practices, and additional instruction if needed.

June 2022-Present Activity Therapy Assistant, Spring Mountain Treatment Center
I facilitate therapeutic groups with patients of different demographics and clinical diagnoses under the supervision of a Certified Therapeutic Recreation Specialist (CTRS). Effectively document interactions with patients and track treatment progress. Create treatment plans for patients based on their diagnosis, preferred leisure activities, and activity level. Adhere to HIPAA policies and procedures. Ensure patient information is accurate and properly filed.

March 2021-Nov. 2021 Emergency Department Chief Scribe, Sunrise Children's Hospital
I oversee the operation of the scribe program by supervising the medical scribes at Sunrise Children's Hospital Emergency Department. I am responsible for recruiting, hiring, termination, quality assurance, scheduling, and timecard adjustments. I execute client goals and communicate with my team to ensure the goals are implemented to reach optimal chart quality and accuracy.

Oct. 2019-March 2021 Emergency Department Medical Scribe, Sunrise Children's Hospital
I efficiently document each patient's visit to the emergency department while adhering to HIPAA. Ensure accuracy with the personal health information in each chart by following up with medical providers on any labs, imaging, or re-evaluations. Demonstrate an understanding of medical terminology as well as utilizing the electronic medical record (EMR) system.

SERVICE AND MEMBERSHIP

Aug. 2020-May 2021 Graduate Rebel Advantage Program
I networked with future and current graduate students in addition to attending workshops that prepared me for graduate school that were related to getting involved in research, improving writing skills, and preparing for the application process.

Aug. 2019-May 2021 Lead Team Coordinator
I organize and lead activities that help students develop their leadership abilities by including activities related to various topics that interest them. This enables students to recognize their own leadership abilities in multiple settings.

Sept. 2017-May 2021 Scientista Foundation: Research and Advocacy Committee
I analyze and interpret statistics to advocate for the inclusion of women in STEMM (Science, Technology, Engineering, Mathematics, and Medicine) fields in addition to assisting with coordinating science outreach programs for high school and middle school students to attend.

RELEVENT COURSEWORK

BIOL 196/Lab General Biology I
BIOL 197/Lab General Biology II
BIOL 304 Molecular Genetics
BIOL 475 Neurobiology
CHEM 121/Lab General Chemistry I
CHEM 122/Lab General Chemistry II
CHEM 347 Lab Techniques of Organic Chemistry I
KIN 101 Athletic Training
KIN 150 Emergency Management
KIN 200 Statistics for the Health Sciences
KIN 223/Lab Anatomy and Physiology I
KIN 224/Lab Anatomy and Physiology II
KIN 245 Anatomical Kinesiology
KIN 312 Motor Control and Learning

KIN 316 Motor Development Across the Lifespan
KIN 346 Biomechanics
KIN 350 Social Psychology of Physical Activity
KIN 391 Exercise Physiology
KIN 424 Kinesiology Professional Development
KIN 475 Seminar in Sports and Fitness Management
KIN 490 Internship in Kinesiology
KIN 492/692 Clinical Exercise Physiology
KIN 657 Physiology of Endurance Performance
KIN 737 Biomechanics of Strength
KIN 750 Research Methods in Kinesiology and Nutrition
KIN 751 Selected Application of Statistical Techniques I
KIN 755 Research on Physical Activity Behavior
KIN 760 Motor Skill and Learning Performance
KIN 765 Neurophysiology of Movement

MATH 181 Calculus I
NUT 340 Introduction to Sports Nutrition
PSY 303 Foundations of Physiological Psychology
PSY 305 Foundations of Perception
PSY 422 Psychopharmacology of Abused Drugs
RAD 100 Introduction to Medical Imaging
REC 530 Therapeutic Recreation Process I: Assessment
REC 603 Historical, Philosophical, and Theoretical Perspectives of Recreation
REC 604 Foundations of Therapeutic Recreation

SKILLS AND CERTIFCATIONS
2023 Certified Inclusivity Assessor (CIA)
2023 Statistical Package for the Social Sciences (SPSS)
2022 Basic Life Support (CPR and AED)
2022 Handle with Care
2022 Verbal De-escalation
2021 CITI program course: Human research, Biomedical IRB course
2021 CareThrough Monthly report (CTMR) and Quality Assurance Program (QAP)
2021 Scribe 101 training for Managers
2019 HIPAA and Harassment Training
2019 Stop the Bleed Course
2013 Microsoft Office (power point/excel/word)

LAB SKILLS
2023 Transcranial Magnetic Stimulation (TMS)
2023 Electromyography
2022 Jebsen Taylor Hand Function Test (JTHFT)
2019 Extraction
2019 Recrystallization
2019 Distillation

2018 Polymerase Chain Reaction (PCR)
2018 Gel electrophoresis
2018 Titrations
2017 Dissections
2017 Microscopy

AWARDS AND RECOGNITION
Fall 2021 Deans Honor Roll
Fall 2020 Deans Honor Roll

REFERENCES
References available upon request.