The Effects of Transcranial Direct Current Stimulation (tDCS) on Fatigue During Maximal Intensity Exercise

By

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Abstract

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Transcranial Direct Current Stimulation (tDCS) of the brain has been shown to have profound effects on many physiological and psychological processes, including effects on the autonomic nervous system and fatigue. **PURPOSE:** The purpose of this study was to investigate the effects of tDCS on parasympathetic and sympathetic nervous system modulation and their influence on a maximum effort fatiguing exercise protocol. **METHODS:** Twenty recreationally active subjects (10 male; 10 female) volunteered to participate in this study. Each individual visited the lab on four occasions. The first visit was a familiarization visit. Visits two through four consisted of a sham treatment, an anodal parasympathetic stimulation treatment, and an anodal sympathetic stimulation treatment, in random order. The subjects sat in a dark, quiet environment for 30-min while receiving the appropriate stimulation. The anode was placed on the T3 area, equidistant between the ear and the CZ point, while the cathode was placed on the contralateral side of the skull, just supraorbital. Following stimulation, the subject completed 50 maximum intensity isokinetic (Biodex medical Systems, Inc., Shirley, New York) leg extensions at an angular velocity of 180°s⁻¹, followed by passive flexion. Autonomic modulation was quantified using time and frequency domain indices of heart rate variability. The data were analyzed using 1x3 repeated measures ANOVAs. **RESULTS:** For the heart rate variability data there were no significant effects for high frequency power (F₁,₈,₃₃,₂ = 0.80, p = 0.44, Eta² = 0.04), low frequency power (F₁,₉,₃₅,₄ = 0.98, p = 0.38, Eta² = 0.05), inter-beat interval (F₁,₈,₃₅,₀ = 0.58, p = 0.55, Eta² = 0.03), root mean square of successive differences (F₂,₀,₃₈,₀ = 1.32, p = 0.28, Eta² = 0.07), variance (F₂,₀,₃₈,₀ = 1.69, p = 0.20, Eta² = 0.08), or SD-1 (F₂,₀,₃₈,₀ = 1.32, p = 0.28, Eta² = 0.07). Likewise, there was no significant effect of tDCS on mean torque (F₂,₀,₃₇,₅ = 0.73, p = 0.49, Eta² = 0.04) or peak torque (F₂,₀,₃₈,₀ = 0.22, p = 0.80, Eta² = 0.01). **CONCLUSION:** In contrast to previously
published studies, the results of this study showed no effects of tDCS on cardiovascular autonomic modulation or fatigue during high intensity exercise. Discrepancies between these results and other studies may be due to differences in stimulation protocol, brain area of stimulation, and/or exercise modality.
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Chapter 1

Introduction

Transcranial Direct Current Stimulation is a non-invasive form of brain stimulation in which neurological excitation (38) in the cell membrane resting potential and changes in firing rate (30, 45) occur as a result of an electrical current from two electrodes placed on the scalp (31). These two electrodes, cathode and anode, allow for two separate types of stimulation, which have been shown to yield opposite results. Anodal stimulation causes depolarization and increases in excitement, while cathodal stimulation causes hyperpolarization and a decrease in excitement (3, 32). These changes in excitement are not great enough to cause direct firing, but rather manipulate the potential nearer or further from threshold (12). Due to the local effects of tDCS, moving either the anode or cathode to a different location can stimulate a different portion of the brain, under the electrode. Dependent upon placement of these electrodes, there is some lateral stimulation that occurs in tissues interconnected to the area directly below the electrode (8, 58). Although not completely understood, the mechanism of action for tDCS has been shown to elicit synaptic and non-synaptic changes to both cortical and sub-cortical structures (46). Additionally, tDCS has been shown to activate pyramidal cells and interneurons which interact via glutaminergic (AMPA) and GABAergic (GABAr) receptors within the initial minute of stimulation which shows an immediate communication between stimulated and nearby tissue (30). Another adaptation that could facilitate neuronal changes is an increase in Cerebral Blood Flow (CBF) with anodal stimulation and decreases in CBF with cathodal stimulation (21, 24, 58). Because of the neuromodulatory effect, plasticity changes, and increased CBF incurred through tDCS (6, 7), this method has been used to decrease the effects of neurological (17) or psychological disorders (2) as well as delaying the onset of fatigue (42). Effects of tDCS are dependent upon frequency and time of stimulation as well as intensity of current (3, 53).

Taking partial responsibility for the changes in excitability and plasticity are changes in membrane proteins and altered ion concentrations across the membrane flowing from anode to cathode (Figure 1) (57). Been et al. showed that Na+ and Ca2+ blockers prevented both long and short
term effects of tDCS (4) which would support the hypothesis that ion channels play an integral part in the response to tDCS. pH changes have also been a proposed mechanism through which tDCS modulates brain activity, specifically causing changes in the levels of N-methyl-D-aspartic acid (NMDA) (26, 50). Similar to ion changes, Been et al. found that NMDA blockers eliminate changes elicited by tDCS, however these only blocked the long term effects, leaving short term effects unaltered (4). Glx (Glutamine + Glutamate) and NAA (N-acetyl aspartate) were also both found to increase, but only on the stimulated hemisphere (11). Of the known mechanisms that act in response to tDCS, ion shifts appear to be largely controlled by the ionotropic AMPA, GABA$_A$, and NMDA receptors which are responsible for changes in membrane potential, excitation, and plasticity, while molecular changes in glutamate (Glu), glutamine (Gln), and NAA could play an integral role in altering the concentrations of membrane proteins (21).

The manipulation of membrane potential elicited by the direct current from tDCS would thus affect each of the aforementioned signaling molecules. For example, cathodal stimulation of select portions of the brain could lead to increased Glu necessary for NMDA receptor (NMDAr) activation. While NMDAr activation via Glu is necessary for many brain functions, over-activation of NMDA receptors can have CNS injury effects like hypoxia-ischemia, trauma, and status epilepticus (10, 33, 43). Similarly, hyper-stimulation of AMPA and Kainic Acid (KA) receptors can have neurodegenerative effects in diseases such as amyotrophic lateral sclerosis (ALS) (22, 33, 47). Manipulating this pathway in the opposite direction would include the use of anodal tDCS as excitatory to the membrane potential, requiring lower levels of glutamate to activate under-excited NMDA receptors. NMDA hypo-function has been linked to abnormal memory function, as well as psychiatric disorders such as Alzheimer’s Disease and psychosis (33).

Figure 1. Mechanisms of action of tDCS. Ionic shifts and transmembrane protein changes result in altered cortical excitability (57).
Neuromuscular fatigue has many similar definitions; as defined by Millet (27), fatigue occurs when there is a decrease in the maximal voluntary force or power of a single muscle or muscle group whether or not the task can be sustained. Enoka and Stuart defined fatigue as, “a general concept intended to denote an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force” (16). “Fatigue is a multi-factorial physiologic process involving continual functional adjustments in the nervous system and the muscle throughout the contractions” (56). It has been previously demonstrated that anodal tDCS on the parasympathetic nervous system increases the power output throughout a submaximal exercise test (42).

Transcranial direct current stimulation has numerous upsides over pharmaceutical treatments for neurological and psychological diseases and disorders, such as few adverse effects, high efficacy, and economical practicality in clinical, research, or individual therapy settings (55). Another reason to further investigate the effects of tDCS is to gain understanding about central and peripheral fatigue and the individual mechanisms of each that combine to decrease optimal functionality of a muscle or muscle group. This is an appropriate area of study not only for determining ways to improve physical performance of athletes, but how to maximize the aerobic and anaerobic abilities of diseased, disabled, and aging individuals (49).

Statement of the Problem

The purpose of this study was to investigate the effects of anodal tDCS of both the sympathetic and parasympathetic nervous system, compared to a sham treatment, looking at the force output during a maximal exercise test. There are currently studies searching for answers regarding tDCS and submaximal exercise (29, 51, 56) as well as maximal exercise and the effect of tDCS on the autonomic nervous system (42). However, there appear to be no studies published comparing sympathetic stimulation to parasympathetic stimulation prior to maximal exercise. Also of interest was the effect of tDCS on the autonomic nervous system (ANS), observed through Heart Rate Variability (HRV).
Hypothesis and Specific Aims

Hypothesis

The hypothesis of this study stated that there would be significant increases in HRV during the parasympathetic stimulation but that the decreased fatigue would occur during the sympathetic stimulation visit due to the short duration and high intensity of the Thorstensson Fatigue Protocol.

Specific Aim #1

To determine if there was a significant difference in fatigue following sympathetic stimulation, parasympathetic stimulation, or a sham treatment.

Specific Aim #2

To determine if there was a significant difference in heart rate variability during stimulation of the sympathetic nervous system, the parasympathetic nervous system, or a sham treatment.

Specific Aim #3

To determine if there was a significant difference in where fatigue during maximal exercise stems from, the central nervous system, or peripheral factors.
Explanation of Terms

Transcranial Direct Current Stimulation (tDCS) – A small dose of electricity (≤ 2.0mA) was sent into the subject’s insular cortex. This electricity causes changes in excitability to occur in the local tissue under the electrode (23). Although tDCS is not a strong enough current to cause an action potential, it does cause a slight depolarization, keeping up a level of excitability for up to an hour following stimulation.

Heart Rate Variability (HRV) – The subject had three electrocardiogram (ECG) electrodes attached, one immediately inferior to the right clavicle, one located on the V5 location, and the reference electrode on the spinous process of the C3 vertebrae. These electrodes read each heart beat and a customized software was used, allowing the time between beats to be calculated in order for the HRV to show the effects of tDCS on the autonomic nervous system.

Surface Electromyography (EMG) – Bipolar EMG electrodes were used to record the action potentials as they move down the length of the muscle fibers of the rectus femoris, vastus lateralis, and vastus medialis.

Maximum Voluntary Contraction (MVC) – The subject kicked out against an isometric lever arm and a connected load cell reads the force produced. This test was run before and after the TFP as a way to determine the source of muscle fatigue.

Evoked Twitch (ET) – In order to determine the type of fatigue that was occurring over the course of the Thorstensson Fatigue Protocol (central or peripheral), a bipolar electrode was utilized to straddle the subject’s femoral nerve. Once the nerve was located, small doses of electricity were sent down the femoral nerve beginning with 30.0mA and increasing until the subject produced a maximal force.
Thorstensson Fatigue Protocol (TFP) – A protocol directed to fatigue the leg extensor muscle group, requiring 50 maximum force kicks from 90° to full extension (0°), while attached to an isokinetic dynamometer. This protocol limited the subject to a fixed angular velocity of 180°s⁻¹, taking 0.5s for the active concentric phase and 0.7s for the passive eccentric phase, allowing for fatigue to be measured quantitatively.

Assumptions

Theoretical Assumptions

1. Subjects honestly and accurately reported all information on the health history questionnaire.
2. Maximal effort was given during each MVC and every TFP repetition.
3. All equipment was attached, calibrated, working, and recording properly.
Transcranial Direct Current Stimulation (tDCS), also known as brain polarization, is a method of neural modulation that has been around for centuries (1). tDCS has been shown to improve motor learning, motor performance, treat depression, Alzheimers, Parkinsons, chronic pain, stroke, drug addiction, and appetite regulation as well as numerous other neurologic and psychiatric conditions (9). It has also been shown that tDCS prior to practicing a motor task can improve speed, accuracy, motor learning and recovery during and after that task (56). Due to these marked improvements, Transcranial Direct Current Stimulation is becoming an often-used tool in both the clinical world, for rehabilitation and therapy, as well as the research world.

Most research to date uses tDCS as a treatment lasting 10-30 minutes at a current ranging from 1.5-2.0mA. Recent literature has proposed that possible acute, repeated exposure to tDCS could also bring about some of the positive effects. One such study (5) compared thirty 30-s rounds of tDCS with 5-s rest between each to an oscillating current performed for the same protocol. This study showed a similar increase when using short bouts of tDCS compared with the slow oscillating current. Bergmann’s study further lends to the idea that increasing excitability in the brain is more a product of modulation of membrane potential, rather than causing actual action potentials(56).

There are numerous upsides to tDCS compared to many pharmacological interventions that produce the same effect. Williams showed that due to localized excitability changes under the electrodes only, tDCS is a way to modulate certain portions of the neuromuscular system without affecting the entire system (56). Another benefit is that there is no lingering effect.
Once the polarization returns to normal, no other effects can be noticed. Although it is somewhat dependent on intensity, density, and duration of the stimulus, corticomotor excitability tends to persist for roughly 1 hour after treatment (29, 35-37).

Heart Rate Variability

The autonomic nervous system (ANS) is a key component for exercise performance, fatigue development in certain diseases, and life itself. Heart Rate Variability (HRV) is a key marker for how the ANS is functioning. Heart Rate tends to be controlled in large part by the temporal cortex. The temporal cortex is involved in motor control, and the left side of the brain is responsible for happy, enjoyable sensation, while the right side tends to be responsible for less pleasant sensations such as pain and heat (42).

Through stimulation of the insular cortex, anodal stimulation of the right side of the brain has shown increased sympathetic cardiovascular responses, while anodal stimulation of the left side of the brain has shown reduced parasympathetic cardiovascular effects (42).

Montenegro recently demonstrated that tDCS above the temporal cortex causes increases in parasympathetic activity at rest in an athletic population (31). Okano expanded this hypothesis to a dynamic exercise test. The results showed that with a 20-minute treatment of anodal transcranial direct current stimulation prior to a dynamic exercise test, parasympathetic activity was increased and exercise performance was improved by ~4% (42). The conclusions that can be drawn from this are that during an aerobic fitness test, parasympathetic stimulation leads to higher vagal modulation, which yields longer parasympathetic withdrawal, leading to a greater HRV, allowing for improved aerobic exercise performance.
Fatigue is most often associated with alterations from homeostatic conditions (40) occurring anywhere between the brain and muscle fibers (54). There are numerous points from which this fatigue can occur. Starting at the brain, cerebral hypoxia has been proposed as a mechanism of fatigue (20), as have motivation, environment, tiredness, and lethargy (54). Fuglevand et al. has suggested that inadequate cerebral excitation could be a primary cause of fatigue (18). Moving down to the level of muscle, Weir et al. suggests that intramuscular levels of lactic acid and H+, lack of Oxygen availability, P, accumulation, and extracellular K+ accumulation, among other peripheral factors can play a role in the reduction of force output by the muscles (54).

1. Neuromuscular Fatigue

There are many different definitions of neuromuscular fatigue. Millet defines it as “....exercise related decrease in maximal voluntary force or power of a single muscle or muscle group whether or not the task can be sustained” (19, 27). Gandevia et al. takes fatigue a step further by discussing the progressive nature, “....the maximal force generating capacity of muscles starts to deline once exercise commences so that fatigue really begins almost at the onset of exercise and develops progressively before the muscles fail to perform the required task” (19). Enoka and Stuart describe it as, “a general concept intended to denote an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force” (16). Fatigue can also simply be described as a decrease in EMG amplitude during either prolonged or high intensity exercise. One thing that most definitions have in common is the lack of a single mechanism.

These individual mechanisms involve central fatigue and peripheral fatigue, as well as central fatigue and peripheral fatigue working in conjunction (25). Neuromuscular fatigue can occur anywhere from the brain to the skeletal muscle. Although they often
accompany one another, central and peripheral fatigues are well recognized as mutually
dependent (27). Fatigue appears to refer to any number of acute occurrences leading to
decreased performance, rather than any one mechanism. Enoka et al. said, “Fatigue is
not the consequence of a single omnipresent mechanism, but rather that it can be
induced by a variety of mechanisms” (16). Task dependency, as this is commonly known
would state that the mechanism responsible for fatigue is a product of the type of task
being completed. This involves such variables as intensity, type, muscle groups,
environment, training status, etc. (54).

Neuromuscular fatigue affects people with diseases and disabilities, both
physiological and psychological, as well as aging individuals, and athletes. For these
populations and many more, understanding the underlying mechanisms of fatigue at
every level is an important task. A further understanding could lead to advances in
prevention and rehabilitation, as well as performance. Fatigue is a multi-factorial
physiologic process involving continual functional adjustments in the nervous system
and the muscle throughout the contraction (56).

2.1 Peripheral Fatigue

A local fatigue effect, peripheral fatigue is often considered to be any fatigue
occurring outside of the central nervous system. Fatigue can occur in the central
nervous system, making its way down to the periphery through the nervous system, or
it can root more strictly in the periphery. Peripheral fatigue is dependent on both the
type of stimulation and the time allowed for recovery following stimulation, and even a
few seconds of recovery can cause significant changes in the level of peripheral fatigue
(27).
2.2 Central Fatigue

Central fatigue involves supraspinal and spinal fatigue (13). It occurs when there is a progressive failure of the nervous system to drive muscle during exercise (13). Twitch interpolation is the main method of exploration into central fatigue (27, 29).

The Central Governor Model (CGM) has been around for sometime, which proposes that the central nervous system is wholly responsible for fatigue in the periphery (39). The CGM proposes that fatigue is less a physical event than it is a feeling or emotion, similar to Rating of Perceived Exertion (RPE) (41), and that power output during exercise, and the decreases seen, are due to signaling from the subconscious brain, rather than the level of muscle itself. This idea stems from the fact that the central nervous system would ultimately be protecting the periphery from working so hard as to cause a catastrophic failure (40, 54).

2.3 tDCS & Fatigue

Transcranial Direct Current Stimulation works to increase excitability in the area directly beneath the anodal electrode (51). As this excitability begins in the brain, it can then move down toward the spinal cord and periphery. Delaying fatigue through tDCS to supraspinal motor cortex could help compensate for decreases in spinal excitability as task duration continues (56). Due to the cortical excitation elicited on numerous brain structures by anodal stimulation (4, 28), the idea of stimulation of the insular cortex could work to alter autonomic nervous system function.

As exposed tissue becomes polarized, excitability is increased via anodal stimulation or decreased via cathodal stimulation (42). These neuromodulatory changes begin in the human insular cortex and the excitation can spread from there. Cogiamanian et al. 2007 completed a study comparing anodal stimulation to cathodal stimulation and sham. The results showed that
anodal stimulation to the cortical motor area induced increasing endurance time for sustained submaximal isometric contractions and also significantly attenuated the decline in endurance time from baseline to postconditioning when compared to cathodal stimulation and the sham treatment (13). Cogiamanian et al. 2007 theorizes that this prolonged endurance time was due to increased cortical excitation, resulting in “increased supraspinal drive by inducing a prolonged facilitation of corticospinal neurons.” In 2013 Williams et al showed that anodal stimulation caused a 6% decrease in fatigue compared with sham while increasing the time to failure by > 30%. There was also a lowered rating of perceived exertion (RPE) during the first half of the task allowing a 38% increase in time at high effort. When completing a maximum exertion cycling protocol (15W + 25W/min until unable to keep 80rpm cadence for >5s) following 20 minutes of 2.00mA anodal transcranial stimulation (parasympathetic), subjects saw significant increases in HRV, peak power output, and time to exhaustion compared to a sham treatment (42).

It has been shown in several studies to date that excitation of the parasympathetic nervous system decreases the fatigue during a submaximal test by either increasing the force produced over a set time (42) or increasing the time to exhaustion (56). The further question that needs to be asked is how will sympathetic stimulation effect fatigue, and will it decrease fatigue over a maximal intensity, short duration exercise test?

3 Thorstensson Protocol

As a means to look at fatigue differences in fiber type of skeletal muscle, Thorstensson and Karlson developed a protocol involving 50 maximal contractions of the knee extensors from 90° to full extension (0°). These extensions take place on an isokinetic dynamometer at set velocity of 180°s⁻¹, with the entire 50 contractions occurring over the span of one minute (52). To assure constant resistance to each contraction the isokinetic dynamometer controls the opposition to each kick. Although the original study was designed to look at fatigue differences between fiber types, it showed to be highly fatiguing to all types of skeletal muscle.
Peak torque will be recorded for each contraction through the protocol and the average of the highest three values from the first ten repetitions (Initial Peak Force) will be compared to the average of the highest three values from the final ten repetitions (Final Peak Force) to find the Fatigue Index(14).

\[ F = \left( \frac{\text{Initial Peak Force} - \text{Final Peak Force}}{\text{Initial Peak Force}} \right) \times 100 \]

4 Evoked Twitch

Evoked twitch is a method of determining the maximal amount of activation an individual can achieve involuntarily. In order to determine where fatigue is occurring, the evoked twitch sends a small electrical stimulus through the femoral nerve, similar to how the central nervous system would send an electrical stimulus. Applied through a superficial bipolar electrode straddling the femoral nerve as it crosses the inguinal crease, Evoked Twitch performed before and after a fatiguing protocol allows for a view as to whether the fatigue is occurring in the central nervous system or closer to the neuromuscular junction.

Millet points out that it is imperative to retest the Evoked Twitch immediately following the end of the Fatigue Protocol because short periods of muscle recovery can have immense effects on the power output from those fatigued muscles (27). Thus it becomes important that the twitch is administered within only a few seconds following the end of the Fatigue Protocol.
Chapter 3

Methods

3.1 Participants

Ten male and ten female subjects volunteered their participation in this study. Prior to participation they were screened for current or past neuromuscular or musculoskeletal injuries as well as any metal implants above the neck, besides common orthotic braces. The study was submitted and approved by The University of Kansas Institutional Review Board to assure protection of all human subjects. Each subject was required to sign an informed consent document as well as complete a health history questionnaire.

3.2 Research Design

The study consisted of four days on which the subjects were asked to visit. The first visit consisted of familiarization with the equipment and procedures of the study. Visits two through four each consisted of one randomized treatment, either parasympathetic stimulation, sympathetic stimulation, or a sham treatment (Fig 3.2). Every visit began with the electrode site preparation, followed by a 30-minute tDCS treatment or sham treatment. On the visits where a 3-minute treatment was administered the subjects had the anode placed on the right side (sympathetic stimulation) or the left side (parasympathetic stimulation). The anode was attached 40% of the way from the most superior point on the skull. The cathode was placed on the contralateral side of the head, just supra orbital (42). There was a 30-second ramp up to constant current of 2.00mA and a 30-second ramp down at the beginning and end of each treatment. During the sham, the subjects received a 30-second treatment so that the initial tingling sensation was present and the subject remained blinded to the treatment. The side of the skull on which the sham was administered was randomized for each subject.
3.2.1 Heart Rate Variability

At the start of the tDCS treatment or sham, heart rate variability was measured through the end of the 30-minute treatment. The room was kept dark and quiet, and the subject was asked not to speak unless necessary. There was a trained member of the research team present at all times, to assure that
the subject remained awake. ECG data was collected with a UFI Model 2122i Bioamplifier (UFI Instruments, Morrow Bay, CA) which fed into a four-channel NI-9215 analog input module (National Instruments Corporation, Austin, TX).

HRV was assessed using five specific variables. To assess the variability between beats, Inter-Beat Interval (IBI) was used as a measure of time between R-waves and Root Mean Square of the Successive Differences (RMSSD) was used to compare adjacent R-R intervals. Low Frequency Power (LF) defined as 0.04-0.15Hz and High Frequency Power (HF) defined as 0.15-0.40Hz were used to determine autonomic nervous system control over HRV. While LF is influenced by both sympathetic and parasympathetic nervous system activity, HF includes only the exertion of the parasympathetic nervous system. Finally, SD-1 was utilized, looking at the standard deviation perpendicular to the line of identity in a Poincare Plot.

3.2.2 Evoked Twitch (ET)

Following tDCS, the subject was moved to the isokinetic dynamometer, where they were safely strapped in using the restraining straps over the contralateral thigh, pelvis, and crossing over each shoulder across the trunk. Subjects remained seated on the isokinetic dynamometer and a bipolar stimulating electrode straddled the femoral nerve as it crosses the inguinal crease. The researcher asked the subject to sit passively as the bipolar stimulating electrode delivered an electrical current causing the leg extensor muscle group to contract. Prior to the TFP a maximum ET was found. The subject’s femoral nerve was located by finding the pulse in the inguinal crease. The cathode and anode of the electrode (Digitimer DS7AH, Hertsfordshire, UK) straddled this point, thus straddling the femoral nerve. This stimulus, beginning at a nearly imperceptible 30mA was increased by 5mA and twitches were administered at these 5mA increments until maximal amplitude was achieved, as recorded during the procedure. Once this maximal amplitude was reached, the Digitimer was increased by ~20% and a series of three twitches were evoked, in order to assure that it was a true maximum (48). Immediately following the TFP another series of three twitches was evoked, beginning at the final amplitude used before the TFP and increased until maximal amplitude was again reached, to see if the fatigue occurring was central or peripheral.
3.2.3 Maximal Isometric Voluntary Contraction (MVC)

After a maximal evoked twitch amplitude was found, subjects remained seated with the right leg flexed at 90°, subjects were asked to kick, giving maximal effort, against an isometric load cell. Three MVC’s were administered immediately following tDCS and prior to the TFP and three more came immediately after the TFP. Strong verbal encouragement was provided to assist the subject in achieving a true maximal contraction.

3.2.4 Thorstensson Fatigue Protocol (TFP)

The fatigue protocol had subjects remain seated and strapped into the Biodex System 3 Pro Isokinetic Dynamometer (Biodex Medical Systems Inc, Shirley, NY). The machine was then switched from isometric mode into isokinetic mode, and the lever arm was set at 180°s⁻¹. Subjects completed 50 maximum effort isokinetic leg extensions from 90° to full extension (0°). Each concentric phase was active, lasting 0.5sec while the eccentric phase was passive until the leg has returned to 90°, lasting 0.7sec (52). Fatigue Index will then be calculated:

$$FI = \left( \frac{Initial\text{Peak}\text{Force} - Final\text{Peak}\text{Force}}{Initial\text{Peak}\text{Force}} \right) \times 100$$

Peak Force was defined for each of the 50 repetitions as the highest point on the curve attained from the torque transducer attached to the isokinetic dynamometer. Using peak force, area under the curve was calculated for the entire fifty repetition protocol. Initial Peak Force is defined as the average of the highest three Peak Force values from the first ten repetitions and the Final Peak Force is defined as the average of the highest three Peak Force values from the last ten repetitions (15).
3.2.5 Electromyography

Pre-amplified, bipolar surface EMG electrodes with fixed center-to-center inter-electrode distance of 20mm, input impedance of 100MΩ, and common mode rejection ratio of 95dB (nominal) were taped over the VL, RF, and VM muscles of the right leg. A single reference electrode was placed on the bony process of the patella. The skin under all electrodes was shaved and cleaned with isopropyl alcohol before the electrodes were attached to reduce inter-electrode impedance and increase the signal-to-noise ratio.

3.2.6 Signal Processing

All EMG (μV) and Torque (V) signals were analyzed using custom programs written for LabView 2011 (National Instruments Corporation, Austin, TX).

3.2.7 Statistical Analysis

All variables were calculated using custom LabView 2011 programs. HRV and TFP variables were analyzed using 1x3 repeated measures ANOVA’s. Evoked twitch and MVC variables were calculated using 2x3 (time x treatment) repeated measures ANOVA’s. A Huynh-Feldt correction for sphericity was applied to all statistical models. For EMG variables during the Thorstensson Fatigue Protocol confidence intervals were calculated to further understanding as to why there was no significant change between conditions.
Chapter 4

Results

4.1 Heart Rate Variability

Descriptive statistics for Heart Rate Variability (HRV) variables can be found in Table 1. Spaghetti graphs of individual responses are seen in Figure 1. The autonomic response to transcranial direct current stimulation showed no significant effect for treatment for High Frequency Power ($F_{1.8,33.2} = 0.80, p = 0.44, \eta^2 = 0.04$), Low Frequency Power ($F_{1.9,35.4} = 0.98, p = 0.38, \eta^2 = 0.05$), Inter-Beat Interval ($F_{1.8,35.0} = 0.58, p = 0.55, \eta^2 = 0.03$), RMSSD ($F_{2.0,38.0} = 1.32, p = 0.28, \eta^2 = 0.07$), Variance ($F_{2.0,38.0} = 1.69, p = 0.20, \eta^2 = 0.08$), or SD-1 ($F_{2.0,38.0} = 1.32, p = 0.28, \eta^2 = 0.07$). These results show that regardless of which side of the brain was stimulated, the autonomic nervous system was unaltered by this direct current transcranial stimulation protocol of the insular cortex.

4.2 Evoked Twitch

Descriptive statistics for all Evoked Twitch (ET) variables can be found on Table 2. Individual responses are shown on spaghetti graphs in Figure 2. ET Torque showed a significant main effect for time ($F_{1.0,19.0} = 26.21, p = 0.01, \eta^2 = 0.58$), but showed no significance in the main effect for condition ($F_{1.9,36.1} = 0.61, p = 0.54, \eta^2 = 0.03$) or the condition by time interaction ($F_{1.9,35.4} = 0.38, p = 0.67, \eta^2 = 0.02$). Evoked Twitch Peak-to-Peak M-Wave Amplitude showed no significant main effect for either time ($F_{1.0,19.0} = 0.07, p = 0.79, \eta^2 = 0.00$) or condition ($F_{1.8,33.4} = 0.07, p = 0.92, \eta^2 = 0.00$), as well as no significant interaction for condition by time ($F_{2.0,38.0} = 0.48, p = 0.63, \eta^2 = 0.02$). These results showed that the torque exerted by subjects following an Evoked Twitch decreased from pre- to post-Thorstensson, showing that fatigue did occur but the level of fatigue did not differ based on whether sham, parasympathetic stimulation, or sympathetic stimulation was received.
4.3 Maximum Voluntary Contraction

Maximum Voluntary Contraction (MVC) descriptive statistics can be found in Table 3. Individual response spaghetti graphs for all MVC variables are found in Figures 3-5. While MVC Torque showed a significant main effect for time (F_{1.0,19.0} = 19.09, p = 0.00, Eta^2 = 0.50), MVC Torque did not have a significant main effect for condition (F_{2.0,38.0} = 0.14, p = 0.87, Eta^2 = 0.01) or a significant interaction for condition by time (F_{1.8,34.6} = 0.84, p = 0.43, Eta^2 = 0.04). There was also no significant main effect for MVC Median Power Frequency for time (F_{1.0,19.0} = 0.75, p = 0.40, Eta^2 = 0.04), MVC Median Power Frequency for condition (F_{1.6,30.4} = 2.60, p = 0.10, Eta^2 = 0.12), MVC RMS for time (F_{1.0,19.0} = 1.08, p = 0.31, Eta^2 = 0.05), MVC RMS for condition (F_{2.0,37.9} = 0.53, p = 0.59, Eta^2 = 0.03), and no significant interaction looking at condition by time for MVC Median Power Frequency (F_{1.7,31.5} = 0.14, p = 0.84, Eta^2 = 0.01) or MVC RMS (F_{1.6,31.3} = 2.37, p = 0.12, Eta^2 = 0.11). This would demonstrate that the TFP appropriately fatigued the muscles, decreasing the MVC Torque from pre- to post-, but that there was no change in MPF or RMS and that the condition did not significantly alter any of the MVC variables.

4.4 Thorstensson Fatigue Protocol

Table 4 shows descriptive statistics from the TFP area under the curve data, and spaghetti graphs showing individual responses to the TFP are found in Figures 6 and 7. The TFP showed no significant main effect for TFP Power (F_{2.0,38.0} = 0.00, p = 1.00, Eta^2 = 0.00), TFP Mean Torque (F_{2.0,37.5} = 0.73, p = 0.49, Eta^2 = 0.04), TFP Peak Torque (F_{2.0,38.0} = 0.22, p = 0.80, Eta^2 = 0.01), Fatigue Index Torque (F_{2.0,57.0} = 0.018, p = 0.98, Eta^2 = 0.01), and Fatigue Index Power (F_{2.0,57.0} = 0.21, p = 0.81, Eta^2 = 0.01), demonstrating that the stimulation condition had no effect on subjects’ performance during the TFP. When looking at the EMG Amplitude over the course of the TFP, the VL slope (F_{1.91,36.20} = 3.50, p = 0.04, Eta^2 = 0.16) showed a significant main effect while the VL intercept (F_{1.66,31.51} = 1.45, p = 0.25, Eta^2 = 0.07) showed no significance from beginning to end for the Vastus Lateralis. Looking at the Rectus Femoris and Vastus Medialis there was no significance found for RF Slope (F_{2.00,38.00} = 0.19, p = 0.83, Eta^2 = 0.01), RF Intercept (F_{2.00,38.00} = 0.25, p = 0.78, Eta^2 = 0.01), VM Slope (F_{1.80,34.10} = 0.37, p = 0.67, Eta^2 = 0.02), or VM
 Intercept ($F_{(1.66,31.61)} = 1.21, p = 0.31, \text{Eta}^2 = 0.06$). Figure 8 demonstrates the changes between condition for all slopes and intercepts. The slightly significant change in VL slope coupled with the lack of significance in any of the other slope and intercept values as well as the large individual variability in Figure 8 would lead to the conclusion that the slope and intercept values do not change based on condition.

 Table 5 shows the 95% Confidence Interval for differences about the mean for EMG Amplitude Slope and EMG Amplitude Intercept for all three of the muscles (VL (Vastus Lateralis), RF (Rectus Femoris), and VM (Vastus Medialis)). Significance was found in the 95% Confidence Interval for VL Slope Sham condition, as well as the Sham, Parasympathetic, and Sympathetic conditions for each of the VL, RF, and VM. The Confidence Interval shows that the range in which the VL Slope during Sham and the VL, RF, and VM Intercepts during all three conditions could be deduced with 95% accuracy.
Chapter 5

Discussion

The present study showed that there were no changes in HRV variables related to the autonomic nervous system when comparing the sham treatment to the parasympathetic and sympathetic treatments. The only significant findings associated with the ET, MVC, and TFP were seen when comparing the ET Torque and MVC Torque by time. This demonstrates that muscular fatigue was occurring during the TFP. However, there was no significant change to any variables when compared by treatment and no interactions when looking at condition by time.

Of particular interest in the current study was the insular cortex which is responsible for numerous functions in the human body including basic emotion, perception of pain, and autonomic nervous system control (34). Since the idea of the current study relates to changes in the autonomic nervous system and effects of fatigue, rather than completing a motor task, the insular cortex was targeted, instead of the motor cortex, as is seen in a majority of tDCS studies (2, 3). While the motor cortex is an appropriate target when looking to rehabilitate from a stroke, or Parkinson’s disease, changes in movement were not of interest in the current study. Instead, changes in insular excitation would theoretically lead to effects on the entire body. The idea was to see how autonomic nervous system stimulation affected fatigue of the periphery.

To our knowledge, this was the first study looking at the effects of transcranial direct current stimulation on fatigue during a maximal anaerobic exercise test. In a previous study, a link was shown between the modulatory effects of tDCS and prolonged maximal exercise. Okano et al. showed that with anodal tDCS to the parasympathetic nervous system (anode on the left side) cyclists had a greater time to exhaustion, a decreased Rate of Perceived Exertion (RPE), and decreased heart rate at submaximal levels. The decreased heart rate is hypothesized to have been in response to a increased parasympathetic modulation and possibly due to a decrease in sympathetic modulation that comes with exciting the left hemisphere of the insular cortex (42). In the present study HRV data was collected during stimulation, prior to exercise. Using this model, no changes in autonomic response were discovered when comparing all three conditions: sham, parasympathetic anodal stimulation, and sympathetic anodal stimulation.
The lack of any significant effect on HRV via tDCS would signify that the transcranial direct current stimulation had no effect on the autonomic nervous system while the subject was quietly seated in a dark, quiet environment. As shown by Okano, the effect was present when HRV was collected during exercise (42). This presents a need for further study to discern whether anodal stimulation to either the parasympathetic or sympathetic autonomic nervous system could result in a potential excitation of the insular cortex that manifests itself only when necessary (i.e. during exercise). A comparative study to collect HRV data during stimulation and during exercise would help to answer this question.

There are a handful of possible reasons that the Okano paper saw significant changes from sham when using parasympathetic stimulation (42) while the current study did not. One possibility could be the training status of the subjects. While the present study looked at recreationally trained individuals, Okano et al. was using “national level road cyclists” (42). Another deviance from the Okano study is the type of exercise. In that study a maximal incremental exercise test was performed, whereas the current study was looking at a maximal anaerobic exercise test. The type of exercise and the portions of the autonomic nervous system excited by each could have played a role in the significance or lack thereof that was incited via tDCS. The size and placement of the anodal pad could have also caused an issue. The smallest recommended pad size is 5x5cm, but the anodal pad used, as included in the stimulation kit, was 6x8.5cm. There is a chance that the large pad diluted the current sent out from the anode, sending weaker signals to a greater area of the brain. Due to the small size of the insular cortex, a majority of these brain areas being stimulated may have been outside of the targeted insular cortex, and thus the excitation was either wasted, or possibly inhibitory to the hypothesized effect. Thus, there are numerous possible reasons why the current study showed no significant changes while one past study (42) did show significance.

As understanding of the structures and specific functions of the brain become better understood, tDCS and its effects will also become more clear. When anodal stimulation is conducted over the T3 area, it is affecting the insular cortex, but what effect is it having on neighboring areas of the brain? Lang et al. found that even anodal stimulation over the T3 area resulted in structures throughout “the dorsal portion of the cerebral hemisphere” being excited and cathodal stimulation of the same area to act on other portions of the brain (24). It appears that this is due to the difference in activation or inhibition at the site directly below the stimulation site, and how that increase or decrease in excitation leads to different signaling throughout the brain based on different cortico-cortical neural networks. As
a whole, the brain depends on functional connectivity of neurons in many regions to for the processing of information (44). The direct effects of tDCS will become much better understood as these excitable signaling pathways in the brain become more fully understood.

Although the current study satisfied the null hypothesis for all autonomic variables, showed no change between conditions for the TFP, and showed no condition by time interaction on EMG variables for Maximum Voluntary Contraction and Evoked Twitch, there was a significant main effect for time in both MVC Torque and ET Torque. As seen through this significant decrease in Torque values for both the MVC and ET, it is clear that fatigue does occur during the TFP. The fifty-kick, maximal effort protocol caused drastic decreases in the torque produced from pre- to post-, but did not show differences based on condition. Despite the lack of changes in autonomic response and the lack of significant differences between treatments, the TFP was validated as a highly effective method for fatiguing the vastus lateralis.

Also of interest is the EMG response during the Thorstensson Fatigue Protocol. No significant changes were observed in the TFP Power or Torque variables, but a slight difference (p = 0.04) was seen in the EMG Slope of the vastus lateralis. To further analyze this the slope values were looked at for the rectus femoris (p = 0.83) and vastus medialis (p = 0.67). As neither showed significance, it was deemed that the change in VL EMG Slope was not meaningful, although it did demonstrate statistical significance. There was no significance for the intercept in any of the three muscles. This shows that there was not a significant change in the slope or intercept values for any of the three muscles when comparing the three conditions. However, when looking at the 95% Confidence Interval the parasympathetic condition for VL Slope and VL Intercept showed to be significantly elevated above the sham with no significant change between sham and sympathetic or parasympathetic and sympathetic. There was no change between any of the conditions for the RF or VM.

Although it was statistically significant, but not meaningful, the fact that the EMG Slope of the vastus lateralis was not equal to zero could suggest that there was a decrease in motor unit activation during the Thorstensson Fatigue Protocol. This decrease in motor unit activation could indicate the occurrence of central fatigue. Further studies are needed to investigate central fatigue, utilizing twitch interpolation.
Conclusions

The present study brings to light numerous other directions for further research in the area of transcranial direct current stimulation and its effects on peripheral function. A link between the autonomic effects during stimulation and during exercise could show some significance as to how the timing of transcranial direct current stimulation affects autonomic performance. On a similar note, when the tDCS is done in relation to exercise it could have effects on performance, for example, what would happen if the insular cortex was stimulated during an exercise test? Also, does the type of exercise make a difference? Okano et al. used an exercise test to exhaustion (42), which is not a completely anaerobic test, whereas the current study used a maximal exercise test lasting exactly one minute. Based on the different mechanisms of fatigue, both central and peripheral, the fatigue seen during these two tests could be stemming from different mechanisms. Does training age or training status alter the effects of tDCS? Would an athlete be more or less apt to show changes in performance after undergoing tDCS? The type of athlete, aerobic or anaerobic could also effect how stimulation alters their physiological response. What would be the response to tDCS when performing a gait analysis, and could this change the gait during a more aerobic performance test? When looking at the Okano study, could the reduction in RPE affect the form of an exerciser as they begin to fatigue, decreasing the chance of injury (42)? Could transcranial stimulation affect the reflexes? If so, there could be numerous possibilities as far as athletes, general population, physical therapy, and the prevention of frailty in aging adults. Mordillo-Mateos et al. compared bilateral electrode placement to unilateral electrode placement (32), which presents the question of how the effects would differ following anodal stimulation with the cathode placed somewhere other than the contralateral supraorbital. Also of interest could be hormonal changes in response to changes in cortical excitability (46). Further research is also warranted in the area of treatment protocol. Valle et al. showed that 5 sessions of tDCS per day showed decreases in pain perception for two weeks, while 10 sessions a day decreased pain for sixty days (53). Similarly, how would prolonged stimulation at a low intensity affect excitability, and with the effect being dependent on both time and intensity, do increases in time or intensity cause differing types of excitability (3)?

Whether it was the type of exercise, the mechanism of fatigue, excitation of surrounding structures, or lack of excitation of the autonomic nervous system, the current study did not see any changes based on treatment. All in all, many of the effects of transcranial direct current stimulation as a
physiological modality for improving the lives and performance of a broad array of individuals is a new and rather untapped area of research that is in need of much further study.
Citations


22. Ikonomidou C, Qin Qin Y, Labruyere J, and Olney JW. Motor neuron degeneration induced by excitotoxin agonists has features in common with those seen in the SOD-1


57. **Zaghi S, Acar M, Hultgren B, Boggio PS, and Fregni F.** Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct

Figure Legend

Figures:

Figure 1:

A) EKG measured Heart Rate Variability High Frequency Power of each individual with mean in bold.
B) EKG measured Heart Rate Variability Low Frequency Power of each individual with mean in bold.
C) EKG measured Heart Rate Variability RMSSD of each individual with mean in bold.
D) EKG measured Heart Rate Variability Variance of each individual with mean in bold.
E) EKG measured Heart Rate Variability Interbeat Interval of each individual with mean in bold.
F) EKG measured Heart Rate Variability SD-1 of each individual with mean in bold.

Figure 2:

A) EMG measured Evoked Twitch Peak-Peak M-Wave Amplitude change during sham visit of each individual with mean in bold.
B) EMG measured Evoked Twitch Peak-Peak M-Wave Amplitude change during parasympathetic visit of each individual with mean in bold.
C) EMG measured Evoked Twitch Peak-Peak M-Wave Amplitude change during sympathetic visit of each individual with mean in bold.
D) Force Transducer measured Evoked Twitch Torque change during sham visit of each individual with mean in bold.
E) Force Transducer measured Evoked Twitch Torque change during parasympathetic visit of each individual with mean in bold.
F) Force Transducer measured Evoked Twitch Torque change during sympathetic visit of each individual with mean in bold.

Figure 3:

A) Force Transducer measured Maximum Voluntary Contraction Torque change during sympathetic visit of each individual with mean in bold.
B) Force Transducer measured Maximum Voluntary Contraction Torque change during sympathetic visit of each individual with mean in bold.
C) Force Transducer measured Maximum Voluntary Contraction Torque change during sympathetic visit of each individual with mean in bold.
Figure 4:
A) EMG measured Maximum Voluntary Contraction Median Power Frequency change during sham visit of each individual with mean in bold.
B) EMG measured Maximum Voluntary Contraction Median Power Frequency change during parasympathetic visit of each individual with mean in bold.
C) EMG measured Maximum Voluntary Contraction Median Power Frequency change during sympathetic visit of each individual with mean in bold.

Figure 5:
A) EMG measured Maximum Voluntary Contraction Root Mean Square change during sham visit of each individual with mean in bold.
B) EMG measured Maximum Voluntary Contraction Root Mean Square change during parasympathetic visit of each individual with mean in bold.
C) EMG measured Maximum Voluntary Contraction Root Mean Square change during sympathetic visit of each individual with mean in bold.

Figure 6:
A) Force Transducer measured Mean Torque during Thorstensson Fatigue Protocol of each individual with mean in bold.
B) Force Transducer measured Peak Torque during Thorstensson Fatigue Protocol of each individual with mean in bold.
C) Force Transducer measured Power during Thorstensson Fatigue Protocol of each individual with mean in bold.

Figure 7:
A) Calculated Torque Fatigue Index during Thorstensson Fatigue Protocol of each individual with mean in bold.
B) Calculated Power Fatigue Index during Thorstensson Fatigue Protocol of each individual with mean in bold.

Figure 8:
A) EMG Amplitude Slope calculated for the Vastus Lateralus during the Thorstensson Fatigue Protocol of each individual with mean in bold.
B) EMG Amplitude Intercept calculated for the Vastus Lateralus during the Thorstensson Fatigue Protocol of each individual with mean in bold.
C) EMG Amplitude Slope calculated for the Rectus Femoris during the Thorstensson Fatigue Protocol of each individual with mean in bold.
D) EMG Amplitude Intercept calculated for the Rectus Femoris during the Thorstensson Fatigue Protocol of each individual with mean in bold.

E) EMG Amplitude Slope calculated for the Vastus Medialis during the Thorstensson Fatigue Protocol of each individual with mean in bold.

F) EMG Amplitude Intercept calculated for the Vastus Medialis during the Thorstensson Fatigue Protocol of each individual with mean in bold.

**Tables:**

Table 1: Descriptive statistics for all Heart Rate Variability measures, broken down by condition.

Table 2: Descriptive statistics for all Evoked Twitch measures, broken down by condition.

Table 3: Descriptive statistics for all Maximum Voluntary Contraction measures, broken down by condition.

Table 4: Descriptive statistics for all Thorstensson Fatigue Protocol measures, broken down by condition.
Figures

Figure 1

A. Heart Rate Variability
High Frequency Power

B. Heart Rate Variability
Low Frequency Power

C. Heart Rate Variability
RMSSD

D. Heart Rate Variability
Variance

E. Interbeat Interval

F. Heart Rate Variability
SD-1
Figure 2

A. Evoked Twitch Peak-Peak M-Wave Amplitude
   Sham

B. Evoked Twitch Peak-Peak M-Wave Amplitude
   Parasympathetic

C. Evoked Twitch Peak-Peak M-Wave Amplitude
   Sympathetic

D. Evoked Twitch Torque
   Sham

E. Evoked Twitch Torque
   Parasympathetic

F. Evoked Twitch Torque
   Sympathetic
Figure 3

A. Maximum Voluntary Contraction Torque
   Sham

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   Sham Pre | Sham Post

B. Maximum Voluntary Contraction Torque
   Parasympathetic

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   Parasympathetic Pre | Parasympathetic Post

C. Maximum Voluntary Contraction Torque
   Sympathetic

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   Sympathetic Pre | Sympathetic Post

Time
Figure 4

A. Maximum Voluntary Contraction Median Power Frequency Sham

B. Maximum Voluntary Contraction Median Power Frequency Parasympathetic

C. Maximum Voluntary Contraction Median Power Frequency Sympathetic
Figure 6

A  Thorstensson Fatigue Protocol Mean Torque

B  Thorstensson Fatigue Protocol Peak Torque

C  Thorstensson Fatigue Protocol Power
Figure 7

A  Fatigue Index (Torque)

B  Fatigue Index (Power)
Figure 8

A. EMG Amplitude
   Slope VL

B. EMG Amplitude
   Intercept VL

C. EMG Amplitude
   Slope RF

D. EMG Amplitude
   Intercept RF

E. EMG Amplitude
   Slope VM

F. EMG Amplitude
   Intercept VM
### Table 1

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Table 4

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<td>-0.15 ± 0.89</td>
<td>-0.25 ± 0.89</td>
</tr>
<tr>
<td>EMG Amp Intercept VL (uV)</td>
<td>20</td>
<td>165.31 ± 104.48</td>
<td>157.82 ± 90.97</td>
<td>173.54 ± 102.40</td>
</tr>
<tr>
<td>EMG Amp Slope RF (uV)</td>
<td>20</td>
<td>-0.14 ± 1.03</td>
<td>-0.09 ± 0.95</td>
<td>-0.02 ± 1.05</td>
</tr>
<tr>
<td>EMG Amp Intercept RF (uV)</td>
<td>20</td>
<td>182.69 ± 93.24</td>
<td>185.95 ± 94.53</td>
<td>189.00 ± 105.13</td>
</tr>
<tr>
<td>EMG Amp Slope VM (uV)</td>
<td>20</td>
<td>0.04 ± 1.41</td>
<td>0.15 ± 1.94</td>
<td>0.27 ± 1.89</td>
</tr>
<tr>
<td>EMG Amp Intercept VM (uV)</td>
<td>20</td>
<td>267.92 ± 136.59</td>
<td>283.24 ± 163.96</td>
<td>298.21 ± 170.94</td>
</tr>
</tbody>
</table>
Effects of Transcranial Direct Current Stimulation on Knee Extensors During Thorstensson Fatigue Protocol

Informed Consent

INTRODUCTION
You are invited to participate in a research study examining the skeletal muscle fatiguing response to a brain stimulation technique that is commonly used to treat psychiatric disorders. This study will be conducted at the University of Kansas, and 20 subjects (10 males & 10 females) are being sought to participate. The Department of Health, Sports, and Exercise Sciences at the University of Kansas supports the practice of protection for human subjects participating in research. The following information is provided to help you make an informed decision on whether or not to participate in the present study. Please feel free to ask any questions.

PURPOSE OF THE STUDY
The purpose of this project is to determine the effect of Transcranial Direct Current Stimulation (tDCS) of the brain on muscle fatigue. Also of interest is the effect of tDCS on the nervous system’s regulation of the heart.

BASIS FOR SUBJECT SELECTION
You are eligible to participate in this study if you meet certain criteria. This criteria includes being recreationally active, between the ages of 18-30, healthy, non-obese (body mass index<28 kg/m²), non-smoking, and free of metabolic or cardiovascular diseases. All subjects will be screened using a health-history questionnaire for contraindications to exercise by American College of Sports Medicine (ACSM) guidelines. Other exclusion criteria include a history of epilepsy or seizures, unhealed fractures, thrombophlebitis (blood clots), recent surgery, recent uncontrolled bruising,
osteomyelitis (acute or chronic bone infection), myositis ossificans (hardened scarring in muscle tissue of the thigh), or past surgery on the right knee.

**PROCEDURES**

A time-line of the testing procedures and an overview of the testing sequence for the pre-testing and test days are presented below. A more detailed description of these procedures can be found immediately after the timeline below. All procedures will be conducted in the Applied Physiology Laboratory and the Neuromechanics Laboratory at the University of Kansas and will be supervised by trained personnel.

**Timeline of Testing Procedures**

**Day 1: (0 hr) (procedures will take approximately 90 minutes)**

- Equipment Familiarization
- Consent Form
- Health History
- Anthropometric Data
- Electrode Site Preparation
- Transcranial Stimulation & Heart Rate Variability
- Evoked Twitches
- Maximum Voluntary Contractions (MVC’s)
- Thorstensson Fatiguing Protocol
- Evoked Twitches
- MVC’s

**Day 2 (> 4 days) (procedures will take approximately 60 minutes)**
Electrode Site Preparation
Transcranial Stimulation & Heart Rate Variability
Evoked Twitches
MVC’s
Thorstensson Fatiguing Protocol
Evoked Twitches
MVC’s

Day 3 (> 8 days) (procedures will take approximately 60 minutes)

Electrode Site Preparation
Transcranial Stimulation & Heart Rate Variability
Evoked Twitches
MVC’s
Thorstensson Fatiguing Protocol
Evoked Twitches
MVC’s

1) Electrode Site Preparation - You will be asked to sit while each of the six electrode sites is cleaned. This process will include shaving the hair from the area, using tape to remove any lotion, sweat, dead skin, or foreign matter, and then cleaning with alcohol. The reason for this is to prevent excess electrical noise that would interfere with the signal from the electrode.

2) Transcranial Stimulation – There will be two electrodes placed on the skull, one on either the right or left side, just above the ear, with the other being placed on the opposite side
forehead, near the hairline. These electrodes will be damp so that no hair removal is necessary, however isopropyl alcohol will be used to clean the hair and scalp below the electrodes, ensuring that hair products, sweat, etc. do not impede the electrodes. Once properly connected, the device will be turned on and the parameters will be set to send a small amount of electricity ($\leq 2.0 \text{mA}$) through your brain. There could be a slight “tickling” sensation, but no discomfort. Stimulation will be given for 30 minutes under immediate supervision of members of the research team. This will occur on all three visits, however each visit will vary. For one visit the electrode will be on the right side of the scalp, for one visit the electrode will be on the left side of the scalp, and for one visit they will be randomly placed, and no current will be passed through the electrode after 30 seconds, this visit will be known as the “Sham.” These three visits will be conducted in randomized order.

3) **Heart Rate Variability** - You will have three electrodes connected to your torso, positioned on the uppermost visible vertebrae, right chest, and left abdomen. This will allow your heart rate to be taken, as a means of gathering information on how tDCS affects the autonomic nervous system. You will not feel anything from these electrodes, as they will simply be gathering information. The electrodes will be removed as soon as the tDCS is finished. This will occur on all three visits.

4) **Evoked Twitch** – Once seated, the researcher will find the pulse in the crease of your hip. This will be found just below the waistband of the shorts on the right side. Digitimer electrode will be placed straddling the area where the pulse can be taken, as that is also the area where the femoral nerve, one of the main nerves in the leg, resides. A brief ($< .05 \text{s}$) low dose electrical current will be sent through the nerve causing the contraction of the quadriceps muscles. A very low dose will be administered at first to assure that you understand how it will feel. From there, increasing doses will be given in 5 mA increments until you have reached the maximum force of contraction. At that point three more doses will be administered at a current just above that which produced the maximal contraction. The three twitches following fatigue will be given at this same dose.

5) **Maximum Voluntary Contraction** – You will be seated on the dynamometer (a chair with an attached lever arm that will read the forces placed against it as you kick), and safely harnessed into the chair. Electrodes will be connected to the right leg, to read the signal
as the tests are performed. First, you will push against a stationary lever arm for ~3 seconds to determine the maximum force level. This will be repeated three times immediately prior to the fatiguing protocol and three times immediately following the fatiguing protocol. Following each maximal contraction there will be a two minute rest, assuring ample time for the subject to recover, allowing for full effort to be given on every MVC. This will occur on all three visits.

6) **Thorstensson Fatiguing Protocol (TFP)** - The TFP is a test that measures fatigue over the course of fifty kicks conducted at a constant velocity of 180° per second. You will be seated in the chair attached to the dynamometer so that the lever arm may be moved as the knee goes through a range of motion from flexed to extended. You will be given five warm-up knee extensions to ensure that the leg extensors are amply prepared to be fatigued. After the fifth warm-up, the test will begin and you will move the knee from flexed to extended fifty times at a constant speed. Following this you will complete the final 3 MVC’s. This will occur on all three visits.

**RISKS**

1) **Electrode Site Preparation** – Some slight scuffs or abrasion of the skin or some slight razor burn are the only risks involved with the preparation of the electrode sights.

2) **Transcranial Stimulation** – The transcranial direct current stimulator is a device that has been used in numerous studies to affect a broad array of physiological, movement and psychological variables. The device sends a small (~ 2 milliamps) electrical current into the brain.

This device is not to be used if you have metal implants in the head (excluding standard orthodontic braces and fillings), or implanted devices such as cochlear implants or cardiac pacemakers.
Transcranial Direct Current Stimulation is a safe technique, but there are some small risks and possible adverse effects which are described below:

- **Slight skin irritation under the electrodes** – The skin beneath the electrodes may be somewhat red for a short period of time. There will be no abrasions or breaking of the skin, just a slight increase in blood flow causing a red appearance.

- **Tingling sensation under the electrodes** – This is the most common side effect of transcranial direct current stimulation. It has been described as a slight sensation and has occurred in a majority of patients during stimulation, but only a few cases linger after stimulation has ceased. In the cases where the sensation did linger, it seems to progressively decrease until the sensation is no longer present, normally disappearing in less than one hour. Other feelings that may accompany stimulation are an itching feeling at either or both electrode sights, almost solely during stimulation or lasting a short time after, mild pain during stimulation with no lingering effects after cessation, or a slight burning sensation during stimulation with no lasting effects after the finish of stimulation have also been reported.

- **Fatigue during stimulation** – In some cases, subjects have suffered a mild to moderate feeling of fatigue. This feeling of mental fatigue is most commonly associated with the stimulation itself, but in a few cases it lasted for a couple of hours after the stimulation.

- **Mild headache following stimulation** – In very rare cases a headache may occur during the stimulation. Somewhat more often, headaches may occur following stimulation, within an hour or so, and can be treated with over the counter pain killers.

- **Seizure** – There have been no reported incidences of seizure. However, due to the tDCCS potential to excite the brain, short lasting, localized seizures could be a side effect. If this were the case, although it could be related to grand mal seizures, these incidences would be more similar to fainting or
swooning from anxiety. For this reason, it is asked that if you have any history of epilepsy, please let the research team know at this time.

- Mood changes – In rare cases some low level nervousness or overexcitement can occur during stimulation. This has not been reported to continue following the stimulation.
- Nausea – Some feelings of nausea have been reported in rare cases following stimulation. These feelings have been shown to last no longer than 2 hours.

A low number of subjects claimed that transcranial direct current stimulation was unpleasant, but most could not tell if the stimulation device was turned on. There were no cases with healthy subjects in which it was requested that the stimulation be terminated.

3) **Heart Rate Variability** – There are no risks involved, as the electrodes are attached to simply read the heart rate.

4) **Evoked Twitch** – This device has been approved for human subject testing by the FDA, and the only risk involved would be the possibility of a slight pinching feeling at the site of the twitch.

5) **MVC** – The only risk involved with the Maximum Voluntary Contractions would be some minimal local fatigue lasting a couple of minutes. Time is given between each MVC to allow this fatigue to disappear. As with all exercise, there may be unpleasant sensations associated with the muscle contractions, and there will elevations in heart rate, blood pressure, and breathing rate. While unlikely, you may also experience an injury of the muscles or joints.

6) **Thorstensson Fatiguing Protocol** – The only risks associated with the Thorstensson Fatiguing Protocol are some local fatigue that may last a couple of hours and the possibility of some minor local muscle soreness in the right leg for up to one day. As with all exercise, there may be unpleasant sensations associated with the muscle contractions, and there
will elevations in heart rate, blood pressure, and breathing rate. While unlikely, you may also experience an injury of the muscles or joints.

7)

**BENEFITS**

We cannot promise any direct benefits to you or others from your taking part in this research. However, possible benefits include an improved understanding of how the nervous system interacts with skeletal muscle function and how the central nervous system has an effect on muscle fatigue.

**PAYMENT TO SUBJECTS**

You will not receive any monetary compensation for participating in this study.

**COMPENSATION FOR INJURY**

The following information is provided in accordance with HEW regulations: “In the event of injury, the Kansas Tort Claims Act provides for compensation if it can be demonstrated that the injury was caused by the negligent or wrongful act or omission of a state employee acting within the scope of his/her employment.”

**IN CASE OF EMERGENCY CONTACT PROCEDURE**

In the event of a research related injury or adverse reaction, please contact Joseph Weir, Ph.D. at 785-864-0784 (office), 515-974-9335 (cell) or Philip Gallagher, Ph.D. at 785-864-0772 (office), 785-550-6300 (cell), or Jake A. Deckert at 620-285-9991 (cell)

**INFORMATION TO BE COLLECTED**

To perform this study, researchers will collect information about you. This information will be obtained from the health history and physical activity questionnaires, heart rate variability, and neuromuscular evaluations. Your name will not be associated in any way with the information
collected about you or with the research findings from this study. The researchers will use a study identification number or initials in place of your name. All of your data will be stored on a password protected computer or in a locked filing cabinet located in a locked office of the applied physiology laboratory. The researchers will not share information about you with anyone outside of the Applied Physiology Laboratory personnel unless required by law or unless you give written permission.

Permission granted on this date to use and disclose your information remains in effect indefinitely. By signing this form you give permission for the use and disclosure of your information for the purposes of this study at any time in the future.

REFUSAL TO SIGN CONSENT AND AUTHORIZATION
You are not required to sign this Consent and Authorization form and you may refuse to do so without affecting your right to any services you are receiving or may receive from the University of Kansas or to participate in any programs or events of the University of Kansas. However, if you refuse to sign, you cannot participate in this study.

CANCELLING THIS CONSENT AND AUTHORIZATION
You may withdraw your consent to participate in this study at any time. You also have the right to cancel your permission to use and disclose information collected about you, in writing, at any time, by sending your written request to: Joseph Weir, Ph.D., University of Kansas, 1301 Sunnyside Avenue, Robinson Center Room 100, Lawrence, Kansas 66045. If you cancel permission to use your information, the researchers will stop collecting additional information about you. However, the research team may use and disclose information that was gathered before they received your cancellation, as described above.

PARTICIPANT CERTIFICATION
I have read this Consent and Authorization form. I have had the opportunity to ask, and I have received answers to, any questions I had regarding the study and the use and disclosure of information about me for the study. I understand that if I have any additional questions about this
study you may call Jake A. Deckert (620-285-9991) or e-mail: jaked6@ku.edu or Prof Joseph Weir (785-864-0784) or e-mail: joseph.weir@ku.edu. I understand that if I have any additional questions about my rights as a research participant, I may call (785) 864-7429 or write the Human Subjects Committee Lawrence Campus (HSCL), University of Kansas, 2385 Irving Hill Road, Lawrence, Kansas 66045-7563, email irb@ku.edu.
I agree to take part in this study titled ‘Effects of Transcranial Direct Current Stimulation on Knee Extensors During Thorstensson Fatigue Protocol’ as a research participant. I further agree to the uses and disclosures of my information as described above. By my signature I affirm that I am at least 18 years old and that I have received a copy of this Consent and Authorization form.

___________________________________    ________________________________
Print Subject’s Name          Signature of subject

__________
Date

___________________________________    ________________________________
Print Name of Person          Signature of Person Obtaining Consent
Obtaining Consent

__________
Date

___________________________________    ________________________________
Print Name of Witness          Signature of Witness

__________
Date
RESEARCHER CONTACT INFORMATION

Joseph P. Weir, PhD  Jake A. Deckert
Department Chair/Primary Investigator  Secondary Investigator
Health Sport and Exercise Sciences  Health Sport and Exercise Sciences
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University of Kansas  University of Kansas
Lawrence, KS 66045  Lawrence, KS 66045

Trent J. Herda, PhD  Philip M. Gallagher, PhD
Secondary Investigator  Secondary Investigator
Health Sport and Exercise Sciences  Health Sport and Exercise Sciences
101 Robinson  101 Robinson
1301 Sunnyside Avenue  1301 Sunnyside Avenue
University of Kansas  University of Kansas
Lawrence, KS 66045  Lawrence, KS 66045
A. JOINT-MUSCLE STATUS (✓ Check areas where you currently have problems)

<table>
<thead>
<tr>
<th>Joint Areas</th>
<th>Muscle Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ) Wrists</td>
<td>( ) Arms</td>
</tr>
<tr>
<td>( ) Elbows</td>
<td>( ) Shoulders</td>
</tr>
<tr>
<td>( ) Shoulders</td>
<td>( ) Chest</td>
</tr>
</tbody>
</table>
( ) Upper Spine & Neck  ( ) Upper Back & Neck
( ) Lower Spine  ( ) Abdominal Regions
( ) Hips  ( ) Lower Back
( ) Knees  ( ) Buttocks
( ) Ankles  ( ) Thighs
( ) Feet  ( ) Lower Leg
( ) Other_______________________  ( ) Feet
( ) Other_______________________

B. HEALTH STATUS (✓ Check if you currently have any of the following conditions)

( ) High Blood Pressure  ( ) Acute Infection
( ) Heart Disease or Dysfunction  ( ) Diabetes or Blood Sugar Level Abnormality
( ) Peripheral Circulatory Disorder  ( ) Anemia
( ) Lung Disease or Dysfunction  ( ) Hernias
( ) Arthritis or Gout  ( ) Thyroid Dysfunction
( ) Edema  ( ) Pancreas Dysfunction
( ) Epilepsy  ( ) Liver Dysfunction
( ) Multiply Sclerosis  ( ) Kidney Dysfunction
( ) High Blood Cholesterol or Triglyceride Levels  ( ) Loss of Consciousness
( ) Allergic reactions to rubbing alcohol

Have you, or anyone in your family, ever been diagnosed with bipolar or other psychiatric disorders? If yes, please explain

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

NOTE: If any of these conditions are checked, then a physician’s health clearance will be required.
C. IMPLANTED DEVICES

Do you currently have any implanted devices that emit an electrical signal (pacemakers, cochlea implants, etc.)

YES_________ NO_________

Do you have any metal implants in above the neck (excluding standard orthodontic braces, fillings, etc.)

YES_________ NO_________

D. PHYSICAL EXAMINATION HISTORY

Approximate date of your last physical examination_____________________________________

Physical problems noted at that time_________________________________________________

Has a physician ever made any recommendations relative to limiting your level of physical exertion?    YES_________ NO_________

If YES, what limitations were recommended?___________________________________________

E. CURRENT MEDICATION USAGE

(List the drug name, the condition being managed, and the length of time used)

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>CONDITION</th>
<th>LENGTH OF USAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F. PHYSICAL PERCEPTIONS

(Indicate any unusual sensations or perceptions. Check if you have recently experienced any of the following during or soon after physical activity (PA); or during sedentary periods (SED))
<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>SED</th>
<th></th>
<th>PA</th>
<th>SED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Chest Pain</td>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart Palpitations</td>
<td></td>
<td></td>
<td>Light Headedness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unusually Rapid Breathing</td>
<td></td>
<td></td>
<td>Loss of Consciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overheating</td>
<td></td>
<td></td>
<td>Loss of Balance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle Cramping</td>
<td></td>
<td></td>
<td>Loss of Coordination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle Pain</td>
<td></td>
<td></td>
<td>Extreme Weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Joint Pain</td>
<td></td>
<td></td>
<td>Numbness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other__________________________</td>
<td></td>
<td></td>
<td>Mental Confusion</td>
</tr>
</tbody>
</table>

**G. FAMILY HISTORY**

(✓) Check if any of your blood relatives . . . parents, brothers, sisters, aunts, uncles, and/or grandparents . . . have or had any of the following)

( ) Heart Disease
( ) Heart Attacks or Strokes (prior to age 50)
( ) Elevated Blood Cholesterol or Triglyceride Levels
( ) High Blood Pressure
( ) Diabetes
( ) Sudden Death (other than accidental)

Have you, or anyone in your family, ever been diagnosed with bipolar or other psychiatric disorders? If yes, please explain (who, what, when, how often, and any medication taken)

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

**H. EXERCISE STATUS**

63
Do you regularly engage in aerobic forms of exercise (i.e., jogging, cycling, walking, etc.)?
YES__________  NO_________

How long have you engaged in this form of exercise? _____ years _____ months
How many hours per week do you spend for this type of exercise? _______ hours

Do you regularly lift weights?
YES__________  NO_________

How long have you engaged in this form of exercise? _____ years _____ months
How many hours per week do you spend for this type of exercise? _______ hours

Do you regularly play recreational sports (i.e., basketball, racquetball, volleyball, etc.)?
YES__________  NO_________

How long have you engaged in this form of exercise? _____ years _____ months
How many hours per week do you spend for this type of exercise? _______ hours