USAARL-TECH-FR--2021-39

Effects of Non-Invasive Brain Stimulation on Soldier's Cognitive and Functional Performance

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This study, USAARL 2018-002, was approved by the U.S. Army Medical Research and Development Command Institutional Review Board on 20 May 2019.

REPORT DOCUMENTATION PAGE

Form Approved
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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
09-09-2021	Final Report	

4. TITLE AND SUBTITLE

Effects of Non-Invasive Brain Stimulation on Soldiers' Cognitive and Functional Performance

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

622787 (6.2)

6. AUTHOR(S)

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5d. PROJECT NUMBER

24220

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

U.S. Army Aeromedical Research Laboratory
P.O. Box 620577
Fort Rucker, AL 36362

8. PERFORMING ORGANIZATION REPORT NUMBER

USAARL-TECH-FR--2021-39

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
810 Schreider Street
Fort Detrick, MD 21702-5000

10. SPONSOR/MONITOR'S ACRONYM(S)

USAMRDC

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

DISTRIBUTION STATEMENT A. Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

[1]U.S. Army Aeromedical Research Laboratory, [2]Goldbelt Frontier, LLC

14. ABSTRACT

Non-invasive brain stimulation has been shown to alter performance in both clinical and healthy populations on cognitive tasks. While performance alterations have generally been shown to result in enhancement, mixed results remain in the literature. Much of the mixed results within the literature have been attributed to the use of different stimulation parameters, targeting of different brain areas, and using a variety of performance measures or assessing different constructs. However, non-invasive brain stimulation is a desirable method for enhancing Soldier performance given the ease of administration and minimal side effects as compared to other forms of performance enhancement (e.g., pharmaceuticals, caffeine). The objective of the current study is to evaluate the effects of transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex in enhancing Soldier cognitive skills and performance on military tasks. A double-blind within-subjects design was used with healthy, rested Soldiers who received non-invasive brain stimulation and performed basic cognitive and operationally relevant tasks. Results of the study found that application of tDCS improved marksmanship performance. Additionally, no significant side effects were found, suggesting tDCS may be a safe method of performance enhancement in Soldiers.

15. SUBJECT TERMS

transcranial direct current stimulation, cognitive enhancement, performance enhancement.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Loraine St. Onge, PhD
UNCLAS	UNCLAS	UNCLAS	SAR	32	19b. TELEPHONE NUMBER *(Include area code)* 334-255-6906

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Acknowledgements

The authors would like to acknowledge the dedication and professionalism of the study physicians. Specifically, we would like to thank Dr. John Campbell, COL Thomas Hair, Dr. John Crowley, LT COL Claire Goldie, and COL Nicole Powell-Dunford for always ensuring the safety and well-being of all who participated in the study. The authors would also like to acknowledge the research technicians who assisted with different aspects of the study, including stimulation monitoring to maintain study blinding and scoring of tasks. These included SGT Ryan Mackie, Mr. Kevin Baugher, Ms. Amanda Hayes, Mr. Bobby Bowers, Mr. Colby Mathews, CPT Jason Boggs, and CPT Carmelo Morabito.

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Table of Contents

Table of Contents (Continued)

List of Tables

List of Figures

Introduction

In response to the changing battlespace and modernization of the Army, methods to improve Soldiers' readiness through the enhancement of cognitive functions are currently being sought. Here, enhancement is defined as improving a Soldier's cognitive and/or functional performance above baseline levels in the absence of exogenous stressors (e.g., sleep deprivation, extended time on task). Methods of improvement include specialized training, augmented reality, and biomedical interventions (e.g., transcranial electrical stimulation, vagal nerve stimulation). While the use pharmaceuticals for optimizing Soldier performance has a long history (e.g., Estrada et al., 2012), the exploration of newer biomedical interventions such as transcranial electrical stimulation (tES) is warranted. Methods of tES, to include transcranial direct current stimulation (tDCS), hold promise for military settings due to their portability, quick time to take effect, short duration of effects, and minimal side effects. Indeed, due to the short amount of time needed for effects to be seen, and that effects often wear off shortly after stimulation is no longer delivered, tDCS may be a method of altering performance that is more controllable than pharmaceuticals.

tDCS is a form of non-invasive brain stimulation that stimulates the brain through the application of a low-intensity electrical current, typically ranging from 1 to 2 milliamps (mA), via electrodes placed on an individual's scalp (e.g., Brunoni et al., 2012; Dedoncker et al., 2016). tDCS is generally thought of as a neuromodulatory intervention as it modifies the neuronal excitability and activity underlying the area of the scalp being stimulated (Nitsche et al., 2008). The neuronal changes that occur following application of stimulation have been associated with changes in behavior (e.g., Coffman et al., 2014; Kuo & Nitsche, 2012; Parasurman & McKinley, 2014) and have been shown to be reversible, with effects typically lasting up to 1 hour (Nitsche et al., 2007), however some studies have found performance effects lasting six hours post-stimulation, and effects on mood and arousal lasting up to 24 hours (e.g., McIntire et al., 2017; McIntire et al., 2014).

Behavioral changes that occur are influenced by the following stimulation parameters: the density of the current, stimulation duration, and the location of the electrodes (e.g., Medeiros et al., 2012; Nitsche et al., 2008). The density of the current refers to the amount of milliamps delivered, with the majority of available studies using current ranges between 1 and 2 mA, where larger densities have generally shown stronger effects, such as increased accuracy on cognitive tasks (e.g., Dedoncker et al., 2016). Stimulation duration refers to how long the stimulation is applied. Many of the current studies include stimulation periods ranging from 5 to 30 minutes (Bikson et al., 2009), with studies demonstrating that the length of the stimulation period affects the length of time before the cortical excitability returns to pre-stimulation levels (e.g., McIntire et al., 2014; Nitsche & Paulus, 2001). Finally, the location of electrode placement affects the subsequent behavioral changes. For example, Matsuo and colleagues (2011) found stimulation applied to the motor cortex significantly improved circle drawing when subjects used their non-dominant hand, whereas many of the reviewed studies on cognitive performance have shown effects on task performance with stimulation applied to the frontal and parietal regions (e.g., Coffman et al., 2014).

To evaluate whether application of tDCS can enhance military performance, operationally significant military tasks measureable within the laboratory and that may benefit from application of tDCS were identified. To this end, a marksmanship and a patrol task were

determined feasible for the study. Next, the cognitive processes used in these tasks were considered. This was a key consideration, as the cognitive processes used for these tasks would determine where tDCS stimulation should be applied. Prior work has shown marksmanship performance to be predicted by visual tracking, sustained attention, motor coordination, spatial processing, divided attention, and mathematical processing (Kelley et al., 2011). Decision-making has also been shown to be an integral cognitive process in accurate performance while performing shoot-don't-shoot portions of marksmanship tasks (Gamble et al., 2018). A Soldier's ability to maintain performance while patrolling an area relies on the Soldier being able to maintain attention to the surroundings, divide and switch attention between the current surroundings and communications from a radio, as well as simultaneously process visual and auditory information, and be able to hold onto and recall pieces of information later (Rábago et al., 2019).

Following the identification of suitable military tasks, the tDCS literature was reviewed for studies where the aspects of cognition pertinent to the identified tasks were assessed using tDCS. The results of this literature review are published in Feltman et al. (2020). These included identifying studies that targeted aspects of attention, working memory, decision making, and cognitive control/flexibility. The review also included identification of a common brain region targeted by the stimulation in order to identify parameters that could have a potential effect on each of the cognitive processes of interest. The left dorsolateral prefrontal cortex (DLPFC) was most commonly seen in the literature and became the main focus of the review for suitable tasks and parameters. Further, the left DLPFC is well supported within the literature as being implicated in the cognitive processes of interest in this study. Miller and Cohen (2001) presented an integrative theory of the functions of the prefrontal cortex where it was outlined that this region of the brain is crucially involved in a multitude of cognitive functions, given its role in the processes of receiving and sending information to various other brain systems, including sensory and motor systems. The specific roles of the left DLPFC is of particular interest, given its association with perceptual decision-making (Philiastides et al., 2011), cognitive control (Vanderhasselt & de Raedt, 2009), and working memory (Barbey et al., 2013). Each of these components are essential for proper performance in the military tasks to be assessed in this study, and were therefore the main focus of literature supporting the application of non-invasive stimulation.

The present study built on previous work by using basic cognitive tasks to assess performance changes with stimulation applied during completion of the tasks, thus providing opportunity for replicating past studies' results. The cognitive tasks completed during stimulation application aid in the transferability of the effects of stimulation to military tasks; participants engaged in cognitive tasks targeting the cognitive processes specific to each military task performed (e.g., attention, working memory). Transfer of the effects of stimulation were evaluated by participants completing military-relevant tasks. A final set of additional cognitive tasks were assessed to evaluate any secondary effects to performance as a result of the stimulation, such as decision making. This was done to assess the potential tradeoffs in using tDCS to enhance cognitive skills. The study aimed to address the following objectives:

Objective One: evaluate whether cognitive and functional performance were improved following the application of tDCS.

Objective Two: document any secondary effects, including medically relevant side

effects, increased risk taking/impulsivity, and performance tradeoffs, with the application of tDCS.

Methods

The U.S. Army Medical Research and Developmental Command Office of Research Protections Institutional Review Board reviewed and approved the protocol for the study. All procedures were conducted according to institutional ethical standards. Participants provided written informed consent prior to participation.

Study Design

A double-blind, randomized, sham-controlled, within-subjects design was used to evaluate the main effect of stimulation on basic and higher order cognitive processes including attention, working memory, decision making, and cognitive control. Carry over and tradeoff effects on performance of military tasks, including marksmanship and a patrol-exertion task, and additional cognitive constructs (e.g., impulsivity, motor inhibition), were assessed. The design included three within-subjects factors (stimulation condition: sham, active-anodal, active-cathodal) and one between-subjects factor (gender: male, female).

Participants

Twenty-seven healthy, active duty, U.S. Army Soldiers (13 females) participated in the study. An additional volunteer consented but did not meet the eligibility criteria. Participants were recruited locally from Fort Rucker, AL through flyers, word of mouth, and distributing flyers via email and approved social media outlets (e.g., Facebook). Potential participants were informed they would be compensated up to $1,200 in a check upon completion of four data collections at the laboratory.

Medically related exclusionary criteria were used and were assessed through self-report and verified by the study physician during the first visit. Potential volunteers were excluded from the study if they had:

- taken any medications which induce drowsiness, such as over-the-counter antihistamines within 24 hours of participation in the study
- any current medical conditions or medications affecting cognitive function or attention
- any history of any attention deficit condition requiring medication
- any history of psychological/psychiatric disorder
- any history of seizures, migraines, or neurological disorders
- history of a head injury involving loss of consciousness
- any metal implanted within the head (e.g., shrapnel, surgical clips) or any implanted devices (e.g., cardiac pacemaker, brain stimulator, hydrocephalic shunt)
- any skin condition on the scalp, such as psoriasis or eczema, or wounds on the head
- currently received hormonal therapy treatments, other than birth control or as determined by physicians
- potential for caffeine withdrawal symptoms that will impede cognitive testing

Materials

The study used a transcranial direct current stimulator device for enhancement, an actigraphy watch to measure compliance with sleep instructions, cognitive tests to assess cognitive functioning, several questionnaires to collect demographic information, sleep-related factors, intelligence, depression and mood states, a simulated gun range to measure marksmanship, and a computerized mock patrol task. The devices and materials used in the study are outlined below.

Devices

Transcranial Direct Current Stimulator.

The HDCStim® device, manufactured by Newronika s.r.l., was used for tDCS to modulate neural activity in the left dorsolateral prefrontal cortex. This device is a Class IIa medical device certified by the Notified Body n.0068 of the European Community. The device conforms to the regulations set forth in the Council Directive 93/42/EEC for medical devices. It conforms to their standards and directions for: general requirements for safety and safety requirements for medical electrical systems (CEI-EV 60601-1), requirements for basic safety and essential performance (CEI-EN 60601-1-2), and programmable medical systems (CEI-EN 60601-1-4). The device has not been approved by the U.S. Food and Drug Administration and was labeled "FOR INVESTIGATIONAL USE ONLY."

Actiwatch®.

The Actiwatch® is a small, lightweight, limb-worn device that uses an accelerometer to monitor the occurrence and degree of motion. The sensor integrates the degree and speed of motion and produces an electrical current that varies in proportional magnitude at a sampling rate of up to 32 Hz. Data were wirelessly downloaded to a reader connected to a personal computer, and the Actiwatch® software to process the data. For the purpose of this study, sleep efficiency, which indicates the amount of time that the wearer is assumed to be "in bed" or attempting to sleep, was used to determine compliance with sleep instructions.

Functional Military Tasks

Standard Marksmanship Task.

In the standard marksmanship qualifying task, participants shot at 40 targets presented sequentially using a rifle. The targets varied in distance, from 50 to 300 meters. The task requires the participant to fire from three positions: prone supported, prone unsupported, and kneeling. The key dependent variable for this task was throughput (accurate shots per second). The weapons simulator used for this task was the Engagement Skills Trainer (EST) 2000 or 3000 (Anthony, 2006). The EST 2000/3000 is a United States Army small arms training device. This device is used in the United States Army Infantry Schools Basic Rifle Marksmanship strategy and allows for weapons training in a simulated environment. As can be seen in Figure 1, a participant fires from one of five lanes at "targets" appearing on a projection screen at a distance of 26' 3" from the firing line. The weapons have been modified to use with the EST 2000/3000 but maintain their form, fit, feel, and function. At the onset of this task participants were familiarized with the weapons simulator, and then zeroed their weapon, or aligned the laser

sensor to the equivalent of the mechanical weapon zero. Zeroing of the weapon took approximately 20 minutes, while the marksmanship task battery required an additional 20 minutes.

Figure 1. EST 2000 set-up.

Patrol Exertion Multitask.

The Patrol-Exertion Multitask (PEMT), developed and validated by Scherer and colleagues (2017), was used to simulate a military patrol. The task required participants to gather information from a 12-minute virtual reality scenario depicting a first-person patrol in Afghanistan while reporting observed improvised explosive device (IED) markers (see Figure 2). The scenario included four "tactical pause" stops for IED marker identification, with a total of 13 targets observed during the scenario. After completing the task, participants were asked 11 post-patrol questions related to their patrol experience (e.g., grid coordinates, clothing colors, time, date, enemy vehicles, presence of IED components, and weapons). The post-patrol questions assessed their attention and memory. While completing the task, participants continuously stepped on a 6-inch exercise step to simulate the demands of a patrol and maintained a heart rate between 65% and 85% of their age-predicted maximum heart rate. Heart rate was monitored using a wireless heartrate monitoring device. Participants wore an Army combat helmet, clear eye protection, and carried a simulated M-4 weapon fitted with an instrumented trigger switch. At nine time points during the scenario an audible tone cue was emitted from a computer speaker. These tones were generated once per minute during periods of both minimal distractions and periods with multiple visual and auditory distractions. Participants were instructed to press

the grip-mounted trigger switch as quickly as possible after each tone. Reaction time to the auditory tone was the outcome measure of interest from this task.

Figure 2. Patrol Exertion Multitask.

Cognitive Tasks

All cognitive tasks (Table 1) were administered electronically using the open-source software package, PsychoPy (Peirce & MacAskill, 2018). Hard copy backups of the electronic were used for questionnaires for one participant due to a technical failure.

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Table 1. Cognitive Tasks Used in the Study

Task	Construct Measured	Description	Time to Complete	Outcomes
Stroop Task (Macleod, 1991)	Selective Attention	In this task, participants were presented with colored words and named the color that the word was printed in and ignored the meaning of the word. Participants completed 10 trials of congruent and incongruent color-word pairs.	3 min	1. Accuracy
Dual n-Back Task (Küper & Karbach, 2015)	Multitasking and Working Memory	In this task, participants were presented with a visual and auditory stimulus simultaneously and were asked whether the current presented stimuli match those presented *n* items previous.	10 - 15 min	1. *n*-level 2. Reaction time (milliseconds [ms])
Digit Span Task (Miller, 1956)	Working Memory	In this task, participants were presented strings of numbers in increasing length and must recall them.	2 min	1. Span size (number recalled correctly)
Rapid Visual Information Processing Task (Bakan, 1959)	Sustained Attention	In this task, participants were presented with a sequence of digits and must detect even-odd-even sequences of digits.	7 min	1 Speed (ms) 2. Accuracy
Shifting Attention Task (Royer, 1971)	Executive Function	In this task, participants were required to determine if a presented set of digits and symbols corresponded with a given key.	2 min	1. Speed (ms) 2. Accuracy
Stop Signal Task (Logan, Schachar, & Tannock, 1997)	Impulsivity Motor Control	In this task, participants responded as quickly as possible to signals identified as “go” signals and to inhibit responses identified as “stop” signals.	3 min	1. Accuracy 2. Speed (ms)
Delay Discounting Task (Koffarnus & Bickel, 2014)	Risk Taking	In this task, participants were presented with a series of questions selecting between an amount of money immediately and a larger amount with a variable time period.	1 min	1. Discount Rate

Questionnaires

All questionnaires (Table 2) were administered electronically with the exception of the Shipley Institute of Living Scale and the Beck Depression Inventory, which were administered in hardcopy. Hard copy backups of the electronic were used for questionnaires for one participant due to a technical failure.

Table 2. Questionnaires Used in the Study

Task	Construct Measured	Description	Time to Complete	Outcomes
Karolinska Sleepiness Scale (KSS) (Kaida et al., 2006)	Sleepiness	The KSS is a single item questionnaire that asks participants to rate how sleepy they feel at the moment.	1 min	1. Sleepiness score
Profile of Mood States – Short Form (POMS-SF) (McNair et al., 1971)	Mood Symptoms	The POMS-SF is a short version of the POMS, a measure of psychological distress and mood. The POMS-SF contains 35 items, in each an adjective is provided and the participant rated how much it describes them using a 5-point Likert scale format.	3 min	1. Tension/Anxiety 2. Anger/Hostility 3. Vigor/Activity 4. Fatigue/Inertia 5. Depression/Dejection 6. Confusion/Bewilderment 7. Total mood disturbance score
Symptom Checklist (Thair et al., 2017)	Physical Side Effects	The physical side effects questionnaire was adapted from a version developed by Thair and colleagues. The questionnaire was filled out prior to and after receiving tDCS to evaluate whether the participant experienced any adverse side effects from the stimulation.	2 min	1. Rating of presence and severity of each symptom listed

Procedure

Data collection for this study began prior to the COVID-19 (December 2019), but was temporarily suspended at the peak (March 2020) of the pandemic. Data collection was able to resume during the pandemic in October 2020, with added precautions and procedures to ensure the safety and well-being of participants and the research team. These included screening participants prior to entering the laboratory for any COVID-19 symptoms and requiring participants to wear cloth masks throughout the duration of study procedures. During two tasks participants were able to remove their masks: the Uses Task, due to the auditory recording, and the PEMT, to maintain comfort while simulating the patrol march. To maintain safety, the research team stepped out of the room during the Uses Task, and a Plexiglas screen was placed between the participant and the research team member during the PEMT (see Figure 2). An additional Plexiglas screen was placed between the participant and the research team member who monitored impedance values during stimulation, as 6 feet of separation could not be maintained.

Figure 3. Impedance monitoring during cognitive task.

Participants visited the laboratory on five occasions to complete study procedures. There was a minimum of 24 hours between each visit. Three of the visits included the stimulation sessions. At each session participants were screened to ensure they met the following study guidelines: (1) obtained at minimum 6 hours of sleep prior to data collection (assessed by Actiwatch®); and (2) refrained from consumption of caffeine, 16 hours, nicotine, 2 hours, and alcohol, 24 hours, prior to the study. Four participants did not meet these guidelines on at least one visit and were rescheduled to complete the study. Two additional participants had an Actiwatch® malfunction and self-reported at least 8 hours of sleep.

Visit One

During Visit One, participants completed the informed consent procedures. Participants then filled out the medical history questionnaire, met with the study physician to ensure they were fit to participate, completed a 5-minute familiarization stimulation and received their Actiwatch®. At this time, participants were given the study guidelines they must adhere to for continued participation (e.g., sleep requirements; caffeine, nicotine, and alcohol restrictions).

Visit Two

During Visit Two baseline data were collected. Participants were first screened to ensure they complied with the study guidelines. Participants who complied with the instructions then completed the following questionnaires: symptom checklist, Karolinska Sleepiness Scale (KSS) and Profile of Mood States – Short Form (POMS-SF). After completion of the questionnaires the participant completed the standard marksmanship task and patrol-exertion task to establish baseline levels of task performance. Participants then completed the following cognitive tasks: Stroop Task, Dual n-back Task, Digit Span Task, Rapid Visual Information Processing Task (RVIP), Shifting Attention Task: Digit Symbol Substitution Task, Stop Signal Task, Delay Discounting Task and Uses Task. Upon completion of the cognitive tasks, participants were thanked for their time and escorted out of the lab.

Visits Three and Four

Visits Three and Four included the stimulation test sessions (one and two) and were identical. Upon arrival, a member of the research team checked for compliance with the study instructions before beginning data collection. Participants then completed the following questionnaires: symptom checklist, KSS, and POMS-SF to establish pre-stimulation values. They then received either active-anodal, active-cathodal, or sham stimulation. Both the participant and research staff were blind to the condition. Stimulation was applied to the left dorsolateral prefrontal cortex (DLPFC) with the reference electrode placed on the contralateral (right) bicep (described below). The scalp and arm were checked for pre-existing damage to the skin before application of the electrodes. The electrodes were then held in place by a rubber strap and 3m™ Coban™ wrap to ensure uniform contact with the skin (see Figure 3). During stimulation, the impedances were monitored by a member of the research team who was not engaged in the data collection to maintain blinding. Impedance values were maintained below 10 kOhms.

While receiving stimulation the participant completed the following cognitive tasks: Stroop Task, Dual *n*-back Task, Digit Span Task, RVIP, and Shifting Attention Task. The order of these tasks were randomized for each testing session. Once both the stimulation and tasks were complete, the stimulator was powered off and the electrodes were removed. The participant then completed the physical side effect, KSS, and POMS-SF a second time to determine if any physical symptoms or sleepiness/mood changes occurred due to the stimulation. Following, the participant completed the marksmanship task and the Patrol-Exertion Multitask. These were counterbalanced amongst participants. Afterwards, the final three cognitive tasks were completed (Stop Signal Task, Delay Discounting Task). Once all the tasks were completed, the participant completed a post stimulation questionnaire to evaluate their detection between active and sham stimulation and whether the participant thought the stimulation altered their performance. Upon

completion of the assessment activities, participants were escorted to the USAARL participant lounge where they could engage in recreational activities for one hour while stimulation effects wore off. Prior to release, a member of the research team checked the participant's vitals, and the participant met with the study physician to be cleared to be released for the day.

Visit Five

Visit Five (stimulation session 3) was identical to the previous two sessions with the exception of returning their Actiwatch®, and filling out a W-9 for taxes purposes. Upon completion of the hour of down time, the participant concluded their participation in the study.

Stimulation Procedures

The HDCStim® device was used to administer 2 mA of direct current to the left dorsolateral prefrontal cortex (F3, shown in Figure 4). Sponge holding bags were soaked in a saline solution for approximately 10 minutes before the rubber electrodes were place inside. A conductive gel was then applied to the side of the electrode, which would contact the skin. The smaller (50 x 50 cm) electrode was applied to F3 using the Beam F3 application. This application uses the distance from tragus to tragus, nasion to inion, and head circumference to determine the precise location of F3. The larger electrode (85 x 60 cm) was applied to the right bicep. The electrode on the head was held in place using a rubber strap in the center and 3M™ Coban™ wrap on the top and bottom to ensure proper contact. The electrode placed on the right bicept was held in place using two rubber straps at the top and bottom of the electrode. Each participant experienced active-anodal, active-cathodal and sham stimulation. Both the participant and the research staff were blind to the condition. Impedances were checked every minute by a member of the research team who was not engaged in data collection. If the impedances went above 10 kOhm, they were to report it to the research staff who would apply additional gel/saline. This never occurred over the duration of the study and adequate impedance values were observed.

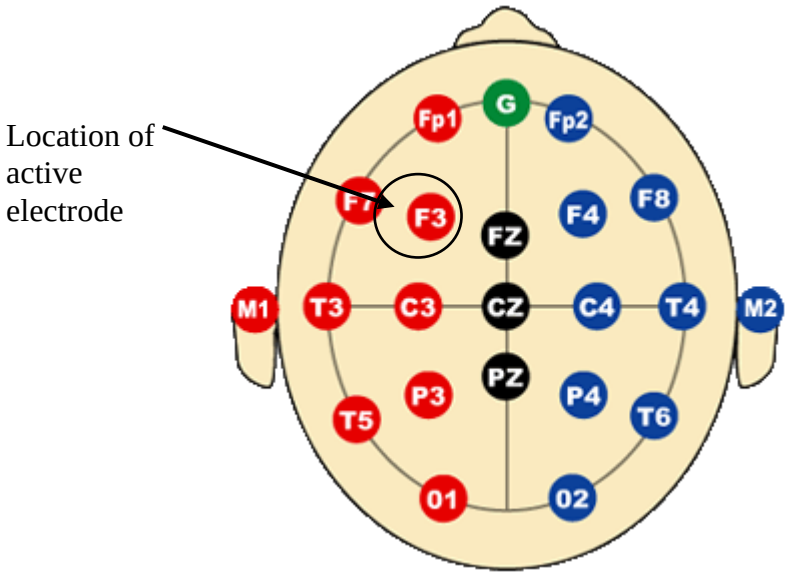

Figure 4. Electrode Placement.

Results

Outliers (standardized values exceeding 3) were removed listwise from the individual analyses. Abstract reasoning score was included in analyses as a covariate (M = 31.85; SD = 4.53). Published normative data (Harnish et al., 1994) for the age groups represented in this study are mean abstract reasoning scores of 29.47 (SD = 7.46) for those 20-29 years and 29.64 (SD = 6.52) for those 30-39 years.

Unless otherwise indicated, performance on each task was evaluated using 2 (gender: male, female) X 3 (conditions: sham, active-anodal, active-cathodal) analyses of covariance (ANCOVAs) (controlling for abstract reasoning score and age). For tasks with multiple, independent outcomes (e.g., reaction time, accuracy), multivariate ANCOVAs (MANCOVAs) were run. Paired comparisons included subsequent paired-samples t-tests.

Objective 1: Evaluate Whether Cognitive and Functional Performance Were Improved Following the Application of tDCS

Stroop task.

Four outliers were removed from the analysis (n = 23). The results did not support an effect of condition on stroop effect, $F(2, 38) = 0.12$, $p = 0.88$.

Digit span task.

One outlier was removed from the analysis (n = 26). The results of the 2 (gender: male, female) X 3 (conditions: sham, active-anodal, active-cathodal) ANOVA support an effect of condition on digit span length, $F(2, 48)) = 5.35$, $p = 0.008$, $\eta^2 = 0.18$. Pairwise comparisons show that active-cathodal tDCS stimulation yielded a significantly lower digit span length than that for the sham ($p = 0.039$) and active, anodal conditions ($p = 0.005$; Figure 5).

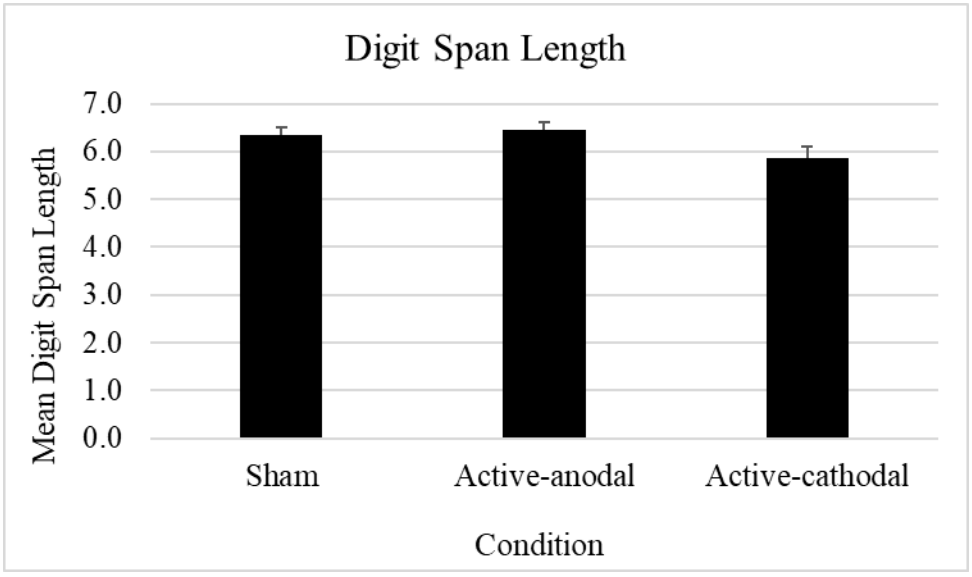

Figure 5. Mean length of digit span by condition. Error bars represent standard error of the mean.

Rapid visual information processing task.

One outlier was excluded from the analyses (n = 26). Separate models were run for the two presentation speeds. A MANCOVA was run with reaction time and d' (sensitivity index) as the outcome measures. In the fast presentation mode, there was a main effect of condition on reaction time, $F(2,44) = 4.86$, $p = 0.01$, $\eta^2 = 0.18$. Specifically, reaction times were faster in the active-anodal than in the sham condition ($p = 0.08$) and in the active-cathodal condition ($p = 0.01$; Figure 6). No significant effects were found for the slow condition, $F(4,76) = 0.44$, $p = 0.78$.

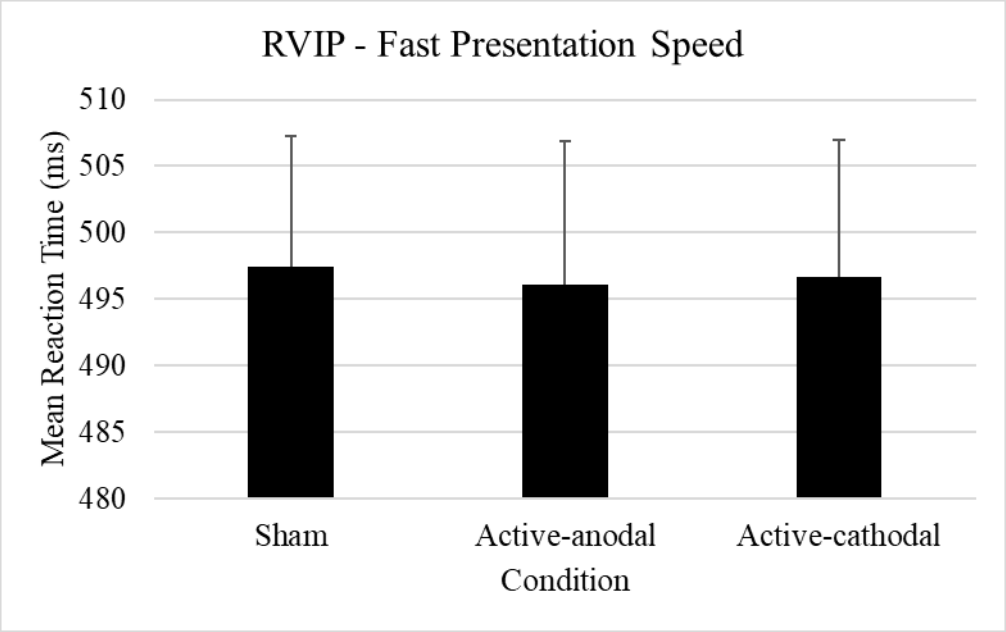

Figure 6. Mean reaction times in the fast presentation mode of the RVIP by condition. Error bars represent standard error of the mean.

Shifting attention task.

Two participants' data were excluded due to outliers. The results of the MANCOVA supported an effect of condition on reaction time, $F(2, 42) = 3.68$, $p = 0.034$, $\eta^2 = 0.15$, and accuracy, $F(2, 42) = 3.85$, $p = 0.029$, $\eta^2 = 0.16$. Planned contrasts showed that reaction times were faster for the active-anodal ($p = 0.034$) and active-cathodal ($p = 0.036$) conditions than the sham condition (Figure 7). Similarly, accuracy was greater in the active-anodal ($p = 0.027$) and active-cathodal ($p = 0.049$) conditions than the sham condition (Figure 8).

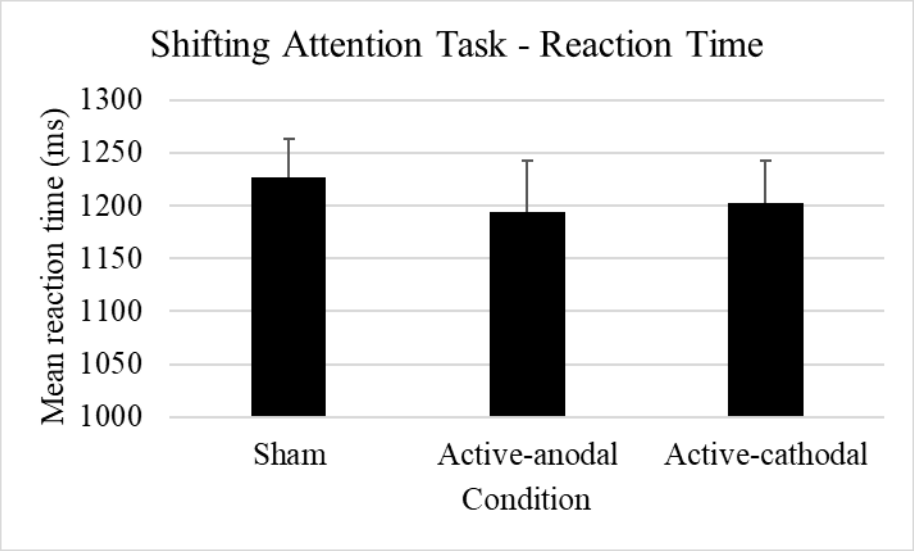

Figure 7. Shifting Attention Task mean reaction times by condition. Error bars represent standard error of the mean.

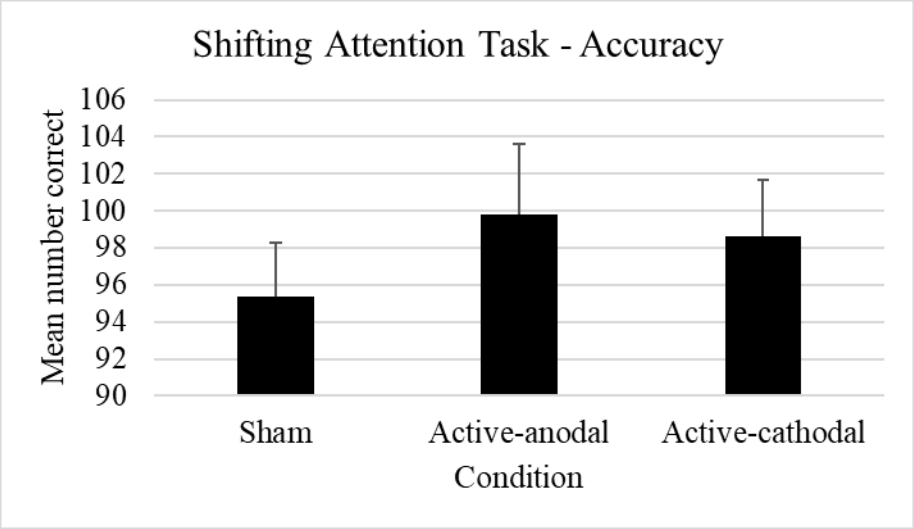

Figure 8. Shifting Attention Task mean accuracy (number correct) by condition. Error bars represent standard error of the mean.

Dual *n*-back task.

Three participants' data were excluded due to outliers. The results of the MANCOVA did not support any effect of condition for reaction time or accuracy relevant to the visual or auditory stimuli (4 outcomes), $F(8, 72) = 0.53$, $p = 0.834$.

Patrol exertion task.

Three outliers were excluded from the analysis. An additional six participants' data were not included due to missing values (technical errors). The results did not support an effect of condition on reaction time, $F(2, 28) = 0.45$, $p = 0.642$.

Marksmanship task.

No outliers were identified; however, seven participants' data were not included due to missing values (technical errors). The covariates includes in the analysis were abstract reasoning score, inattention score (ADHD scale), and baseline marksmanship performance (total number of hits). Age and gender were excluded given that they did not vary systematically with performance. The results showed an effect of condition on throughput (hits/second), $F(2, 32) = 3.67$, $p = 0.037$, $\eta^2 = 0.19$. Specifically, performance in the active conditions ($p < 0.05$) was better than the sham condition (Figure 9).

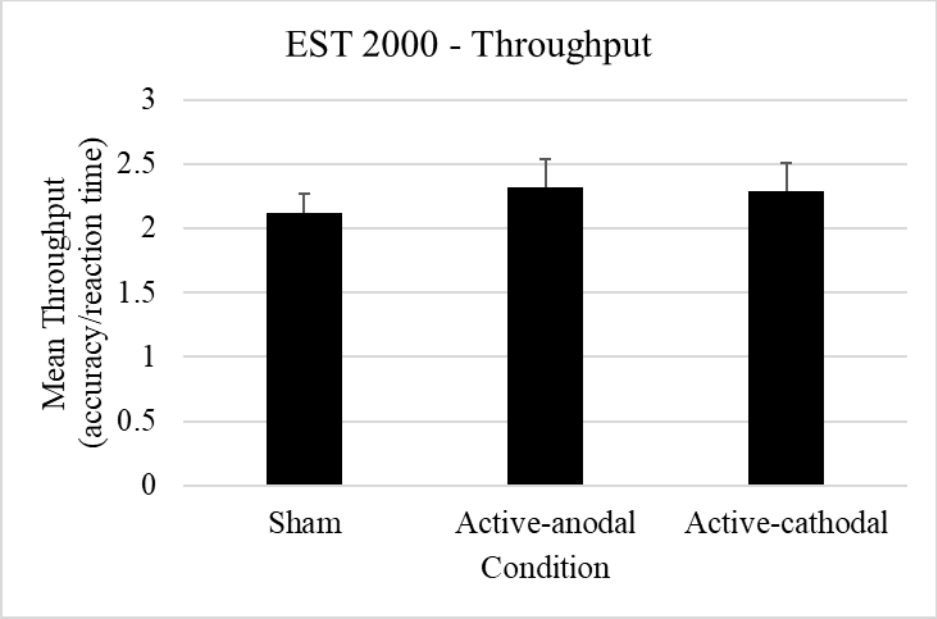

Figure 9. Mean throughput (accuracy/reaction time [s]) by condition. Error bars represent standard error of the mean.

Objective 2: Document Any Secondary Effects, Including: Medically Relevant Side Effects, Increased Risk Taking/Impulsivity, and Performance Tradeoffs, With the Application of tDCS

Delay discounting task.

Five outliers were identified and excluded from the analysis. The analysis yielded a significant effect of condition on the primary outcome, discounting rate (k), $F(2, 36) = 8.98$, $p = 0.001$, $\eta^2 = 0.33$. Planned contrasts showed that the discounting rate was significantly greater in the active-anodal condition than the sham condition ($p = 0.008$; Figure 10).

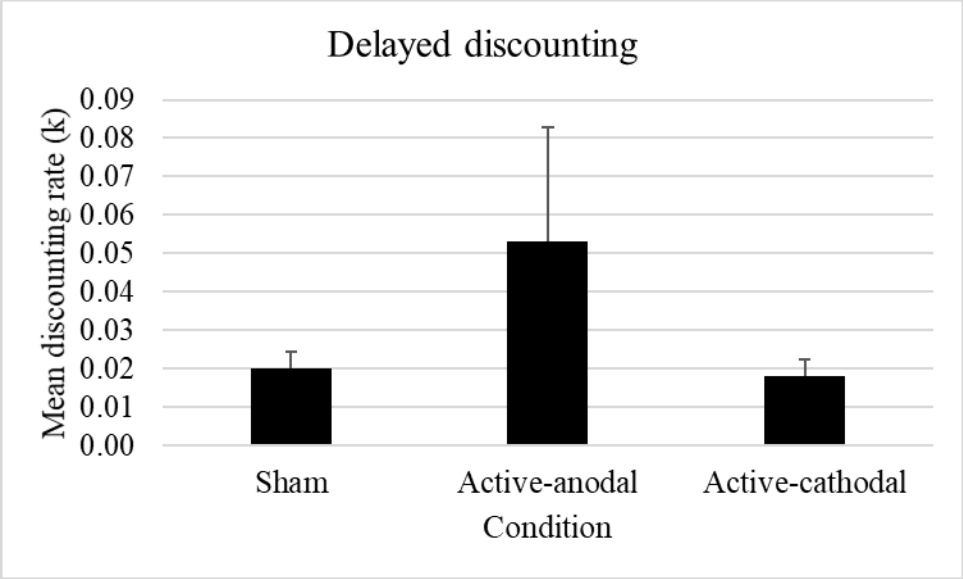

Figure 10. Delay Discounting Task mean discounting rate by condition. Error bars represent standard error of the mean.

Stop signal task.

Four outliers were identified and excluded from the analysis. The results did not support an effect of condition, $F(2, 36) = 1.57$, $p = 0.23$.

Profile of mood states.

All seven subscales (tension, anger, fatigue, depression, confusion, vigor, esteem-related affect) were included as outcome measures in the MANCOVA. Four participants' data were excluded due to missing values. There was a significant effect of condition on the fatigue subscale, $F(2, 38) = 3.83$, $p = 0.031$, $\eta^2 = 0.17$. Planned contrasts showed that fatigue was significantly greater for sham than the active-cathodal condition (Figure 11). Fatigue scores increased from pre- to post-testing for the sham condition whereas fatigue was stable for the active conditions.

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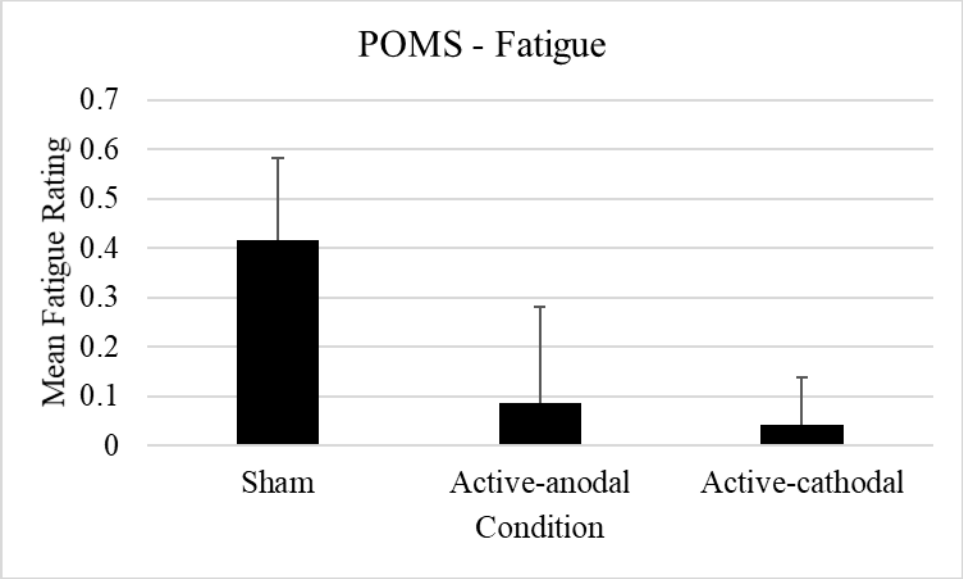

Figure 11. Profile of Mood States mean fatigue ratings by condition.

Karolinska sleepiness scale.

One participant's data were excluded from this analysis for missing data. The results did not support an effect of condition on sleepiness scores pre- to post-testing, $F(2, 44) = 0.20$, $p = 0.82$.

Symptom checklist.

The symptom checklist was administered at two time points, pre- and post-stimulation.

Table 3. Frequencies of Symptoms Reported by Condition Following Stimulation and Data Collection. Severity was rated on a scale from 1 to 10

Symptom	Sham	Active-Anodal	Active-Cathodal
Nervousness or Anxiety	0	0	0
Acute mood change	0	0	0
Headache	0	0	1
Severity rating			1
Nausea	1	0	0
Severity rating	3		
Neck pain*	0	0	0
Increased heart rate	0	0	0
Back pain*	0	0	0
Blurred vision	0	0	0
Scalp irritation	0	2	1
Severity rating		2 (n = 1) 3 (n = 1)	1
Tingling	1	5	5

Severity rating	1	2 (*n* = 2) 3 (*n* = 3)	1 (*n* = 2) 2 (*n* = 3)
Itching	3	3	2
Severity rating	1 (*n* = 1) 2 (*n* = 1) 3 (*n* = 1)	1 (*n* = 1) 2 (*n* = 1) 3 (*n* = 1)	1 (*n* = 1) 2 (*n* = 1)
Burning sensation	0	3	2
Severity rating		1 (*n* = 3)	1 (*n* = 1) 2 (*n* = 1)
Hot flush	0	0	0
Dizziness	0	0	0
Fatigue	0	1	0
Severity rating	0	1	0
Difficulty Concentrating	1	3	1
Severity rating	2	2 (*n* = 2) 8 (*n* = 1)	4
Pain under electrode(s)	0	1	1
Severity rating		1	2

*2 participants indicated symptoms pre-stimulation

Discussion

The objectives of the current study included evaluation of whether cognitive and functional performance were enhanced during or following, respectively, the application of tDCS, and to document any secondary effects resulting from tDCS application. The results support enhancement during tDCS stimulation on measures of working memory, executive function, and sustained attention. Additionally, enhanced marksmanship performance was seen following stimulation. All observed effect sizes are considered large in magnitude given accepted, published "rules of thumb" (Cohen, 1988). Secondary effects demonstrated include increases in impulsivity during stimulation as well as physical symptoms (primarily skin irritation and tingling).

Performance

Regarding cognitive performance, the RVIP, and the Shifting Attention Task both showed improved performance with the application of active tDCS. More specifically, during the RVIP participants had faster reaction times when they received both the active-anodal and active-cathodal tDCS when the stimuli presentation mode was fast (one per second). Similar was found for the Shifting Attention Task, which both active-anodal and cathodal applications resulted in faster reaction times and improved accuracy. These findings are in line with much of the recent literature regarding tDCS application, such that active-anodal and active-cathodal stimulation have similar effects on cognitive functions. Previous literature reported opposite effects, where anodal stimulation had an excitatory effect and cathodal an inhibitory effect (for a review, see Jacobson et al., 2012). However, it appears that this differentiation between electrodes is only reproducible within the motor cortex, whereas cognitive functions have less reliably demonstrated such effects. One unexpected finding regarding the cognitive performance

was that of the Digit Span Task. In this task, participants performed slightly worse when receiving the active-cathodal stimulation compared to receiving the sham and active-anodal conditions. This may be due to the aforementioned inhibitory effects of cathodal stimulation.

Finally, regarding functional performance, there was improved performance found on the marksmanship task. Specifically, participants demonstrated improved throughput when receiving active stimulation (anodal and cathodal) compared to sham stimulation, whilst controlling for abstract reasoning scores, inattention, and baseline marksmanship performance. The potential moderating variables (individual differences in abstract reasoning ability, inattention propensity, and baseline marksmanship skill) align with past research. It is reasonable to assume that enhanced would be limited or prohibited in those who are already high performing in terms of skill and ability. Regarding inattention, recent research has demonstrated that individuals who measure high on inattention benefit from tDCS application when completing an attentional task (Sikström et al., 2016). While we hypothesized that the active-anodal condition would enhance performance, we did not anticipate seeing such an effect in the active-cathodal condition. Further evaluation of this finding and the role of moderating variables is necessary prior to drawing conclusions regarding tDCS stimulation and marksmanship performance.

Taken together, the results of the current study suggest that application of active tDCS at 2 mA for 30 minutes to the left DLPFC improves some cognitive performance, which may transfer to marksmanship throughput performance. However, the improved performance was minimal, leaving to question whether it is practically significant. Considerations for the practical significance include the environmental conditions (low stress, not entirely realistic), and skill level of participants. In a more realistic setting, the performance changes may be greater. Additionally, there may be other individual difference factors moderating performance that were not explored here.

Side Effects

Two performance measures were included to evaluate possible performance tradeoffs that could occur with the application of stimulation. These included a measure of risk taking, specifically impulsivity (delay discounting task), and a measure of impulsivity/motor control (stop signal task). Of these two tasks, effects from the stimulation were noted only in the delay discounting task. Participants had significantly higher discount rates when receiving active-anodal stimulation. This may be an unwanted side effect of active-anodal tDCS, given that higher discounting rates are associated with increased impulsivity (e.g., Odum, 2011). Although an individual's discounting rate typically reflects a tendency of engaging in a variety of impulsive behaviors (e.g., drug abuse, gambling) (Koffarnus & Bickel, 2014), our participants only demonstrated the increased discount rate during active-anodal stimulation. This is a concern for the use of tDCS in a military population where an increase in risk taking is typically undesirable. However, others have found the opposite effect, where anodal tDCS to the left DLPFC decreased discounting rates (e.g., He et al., 2016). Further work is needed to fully understand this potential side effect and its possible effects on decision making.

Changes to mood were also evaluated as a possible side effect of stimulation. Here we found changes in the fatigue subscale of the POMS-SF, where fatigue scores increased from pre- to post-stimulation when participants received sham stimulation, but remained stable when participants received both active stimulations. This finding is similar to that of McIntire et al.

(2014), who compared the effects of tDCS to caffeine during a 30 hour extended wakefulness study. In their study, they found that tDCS application lead to improved subjective ratings of fatigue compared to caffeine. However, no significant changes were found in sleepiness scores on the KSS.

Finally, regarding the symptoms checklist, participants reported experiencing more symptoms when receiving active stimulation condition compared to the sham stimulation. However, only two subjects reported ratings exceeding the value required for physician evaluation (severity rating of 5 or greater). Symptoms that participants experienced during the active stimulation conditions included headache, scalp irritation, tingling, itching, burning sensation, difficulty concentrating, and pain under the electrodes. During sham stimulation, one participant reported experiencing nausea, one tingling, three itching, and one difficulty concentrating. The experience of these side effects were expected, and none resulted in the discontinuation of stimulation nor medical intervention. Following stimulation, all participants' skin were inspected upon removal of electrodes. One participant developed a rash on the bicep where the electrode was placed. The study physician inspected the rash and consulted with the participant, and determined that the rash was due to an interaction with the saline/conductive gel and a new skin lotion being used by the participant. The rash cleared up prior to the participant being released for the day. One participant mentioned feelings of fatigue prior to release; fatigue symptoms did not persist beyond a couple of hours.

Limitations

Several limitations were noted during the study. In particular, the functional military tasks used had several associated limitations. The PEMT was limited in that we used it multiple times over the course of the study, increasing the likelihood of learning effects. As such, we only examined the reaction time outcome and not performance related to memory. The marksmanship task was also limited in that several participants had very poor marksmanship to begin with. Future studies should consider pre-screening marksmanship ability.

Conclusions

Application of tDCS may be a method of enhancing Soldier cognitive readiness with minimal unwanted side effects. Specifically, tDCS applied to the left DLPFC at 2 mA for 30 minutes during cognitive tasks, resulted in improved throughput on the marksmanship task. The method of tDCS application chosen for this study, where participants received tDCS prior to completing the military functional tasks, was done to better replicate what is currently (based on the available technology) a potential method for using tDCS in the field. Although we were able to demonstrate the transferability of the performance effects of tDCS from cognitive tasks to a military task, further research is needed to refine the use of tDCS in an attempt to achieve more practically significant performance changes.

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Appendix A. In-House Questionnaires

PHYSICIAN SCREENING CHECK LIST

TODAY'S DATE _____/_____/_____
YOUR INITIALS (Study Physician) _____
SUBJECT NUMBER _____

Are you on active military duty? ..... **YES NO**

Are you National Guard or Reservist? …….. **YES NO**

If yes, circle which…… **NG Reserve**

I am going to ask you a series of questions. For your own safety, please answer all of the questions honestly and to the best of your knowledge. Let me know if you don't understand a question.

DATE OF BIRTH _____/_____/_____
day month year
AGE ..... _____ **(must be 19-40 years of age)**
HEIGHT ..... _____ ft/inches (or cm)
WEIGHT ..... _____ lbs (or kg)
RIGHT or LEFT-HANDED? ..... **RIGHT LEFT BOTH**

DEPENDENCE HISTORY

Have you ever been diagnosed with a psychiatric illness?	**Yes**	**No**
Have you ever been hospitalized for a psychiatric or psychological reason?	**Yes**	**No**
Have you ever used or abused illegal or prescription drugs?	**Yes**	**No**
Have you ever been under medical care for an addiction of any kind?	**Yes**	**No**

Disqualify if subject has a history of drug abuse or history of addiction.

ALCOHOL USE

On average, how many beers do you drink per week? _____
On average, how many glasses of wine do you drink per week? _____
On average, how many mixed drinks or shots do you drink per week? _____

Disqualify if more than 6 beers/week or 4 glasses wine or 4 mixed drinks/week

NICOTINE USE

Do you use products containing nicotine? ..... **YES NO**
– including e-cigarettes, patches/gum, cigars
If Yes, what? _____
On average, how many times per week do use? _____
On average, how long before you experience withdrawal symptoms? _____

MEDICATION USE

Are you currently taking any prescription drugs? ..... **YES NO**

If Yes, what? _____

For what? _____

Are you currently taking any over-the-counter drugs? ..... **YES NO**

If Yes,what? _____

For what? _____

Are you currently taking any vitamins or dietary supplements? ..... **YES NO**

If Yes, what? _____

For what? _____

Study Physician will determine whether any of the above is exclusionary

MEDICAL HISTORY

Have you ever had, or do you now have: (Y=YES N=NO D=DON'T KNOW)

IF YES, obtain (1) Type; (2) Mo/Yr of occurrence; (3) Is it current?

Y N D ..... Attention Deficit Disorder?

Y N D ..... Neurocognitive Disorders (e.g., cognitive disabilities)?

Y N D ..... Psychiatric Disorders (e.g., depression, anxiety, bipolar)?

Y N D ..... Head injury?

Y N D ..... Loss of consciousness, including fainting or passing out?

Y N D ..... Asthma?

Y N D ..... Have you ever had a seizure?

Y N D ..... Do you suffer from migraines?

Y N D ..... Do you have any metal in your head (other than inside the mouth) such as shrapnel or surgical clips?

Y N D ..... Do you have any implanted devices (e.g., cardiac pacemaker, brain stimulator)?

Y N D ..... Head wound that has not completely healed?

Y N D ..... Neuritis?

Y N D ..... Eye trouble?

Y N D ..... Do you wear glasses or contacts?

Y N D ..... Ever had an adverse reaction to tDCS or any other brain stimulation technique (e.g., TMS, tRNS)?

Y N D ..... Bled excessively after injury or tooth extraction?

Y N D ..... Skin diseases, particularly on your scalp?

Y N D ..... Coughed up blood?

Y N D ..... Shortness of breath?

_____

Y N D ..... Pain or Pressure in the chest? (circle which)

Y N D ..... Rapid or Pounding heartbeat? (circle which)

Y N D ..... High or Low blood pressure? (circle which)

Y N D ..... Any condition that may interfere with placing the reference electrode on your upper right arm? Such as a recent injury or metal (e.g., shrapnel, surgical clips)?

Y N D ..... Bad reaction to drugs, medicines, or serum? (circle which)

Y N D ..... Have you ever been hospitalized for injury or illness?
If YES, what/when?

Study Physician will determine whether any of the above is exclusionary (check whether cleared for study or did not qualify and sign.

_____ _____ _____

Cleared ***DNQ*** ***Physician Signature & Date***

Subject ID: _____ Test session: _____ Research Team Member Initials: _____

Post Stimulation Questionnaire

Please select a response that most accurately reflects your agreement with the statements below.

1. The brain stimulation affected my performance.

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

2. After receiving brain stimulation my performance was better.

    ___ Strongly Disagree

    ___ Disagree

    ___ Agree

    ___ Strongly Agree

    ___ N/A (stimulation did not have any effect on my performance).

3. After receiving brain stimulation my performance was worse.

    ___ Strongly Disagree

    ___ Disagree

    ___ Agree

    ___ Strongly Agree

    ___ N/A (stimulation did not have any effect on my performance).

4. Do you think that you received active stimulation during your participation today?

___ Yes

___ No

Subject ID: _____ Test session: _____ Research Team Member Initials: _____

Post Study Questionnaire

Please select a response that most accurately reflects your agreement with the statements below.

1. I could easily learn how to use tDCS.

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

2. It is a good idea for soldiers to use tDCS as a cognitive enhancement tool in operational environments:

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

3. Most of my fellow soldiers will welcome the fact that I use tDCS as a cognitive enhancement tool.

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

4. The military will encourage the use of tDCS as a cognitive enhancement tool:

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

5. I feel comfortable with using tDCS in an operational environment:

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

6. I intend to use tDCS as a cognitive enhancement tool in operational settings if/when the military makes it available to soldiers.

    ___ Strongly Disagree

    ___ Disagree

    ___ Undecided

    ___ Agree

    ___ Strongly Agree

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