Bihemispheric Transcranial Direct Current Stimulation with Halo Neurostimulation System over Primary Motor Cortex Enhances Rate of Force Development in an Isometric Lateral Pinch Force Task

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ABSTRACT: Transcranial direct current stimulation (tDCS) is a noninvasive technique that modulates motor function. Previous research has shown that tDCS administered over the primary motor cortex (M1) enhances performance of complex motor tasks in both healthy and clinical populations. Despite these promising results, the current methods of implementing tDCS are typically inconvenient to administer and are generally only available in a lab setting. The rationale of this study was to explore the effects of tDCS on motor function in healthy populations as part of a development program leading to a novel wearable device that offers efficient and anatomically precise neurostimulation outside of the laboratory setting. To this end, the Halo Neurostimulation System was utilized to deliver bihemispheric tDCS to the primary motor cortex (M1) of healthy, right-handed human participants during an isometric pinch force (PF) task, in which participants applied maximum isometric force to a pinch gauge with their non-dominant hand. tDCS was observed to facilitate motor performance; specifically, tDCS was associated with a faster rate of force development (RFD). This study indicates that tDCS delivered via the Halo Neurostimulation System may be an effective and safe method to improve force generation in healthy populations.

INTRODUCTION

Efficient motor function plays a crucial role in facilitating both everyday tasks and more powerful movements, such as those required for weight training or cardiovascular exercise. Previous research has shown that motor exertion requires distal muscular contraction as well as sufficient neural drive (Folland *et al*., 2014). Neural drive refers to the electrical signal sent from the central nervous system to the muscle, which drives the recruitment of motor units and causes the muscle to generate force. The primary motor cortex (M1) plays a key role in supplying this consistent, ongoing neural input to muscles and maintaining maximal force exertion in the presence of fatigue (Dutta *et al*., 2015).

Transcranial direct current stimulation (tDCS) is a noninvasive technique that modulates cortical excitability via electrodes in humans. Through the induction of weak intracerebral ionic current between a positively charged anode and a negatively charged cathode, tDCS has been shown to increase the excitability of M1 (Nitsche *et al*., 2005). Previous research has also indicated that tDCS over M1 can enhance motor performance of a variety of muscle groups in both healthy and clinical populations. For example, Hummel *et al*. (2010) found improved performance on the Jebsen-Taylor Test (JTT) after anodal tDCS over the left primary motor cortex in healthy right-handed subjects. The Jebsen-Taylor Test is a seven-part test that evaluates the speed of hand functions used in daily activities. In this study, subjects maintained functional gains during, immediately after, and for at least 30 minutes after stimulation. In a different study, it was found that anodal tDCS over M1 increased maximal pinch force (PF) and shortened reaction time (RT) in stroke patients performing simple hand motor tasks (Hummel *et al*., 2006). Tanaka *et al*. (2009) found that anodal tDCS transiently enhanced maximal leg PF during its application. A variety of papers have shown that anodal tDCS over M1 increases time to task failure during fatiguing contractions with the elbow flexors (Cogiamanian *et al*., 2007, Williams *et al*., 2013). Importantly, elbow flexor studies have shown that anodal tDCS alters motor unit recruitment, supporting the hypothesis that manipulation of brain excitability via tDCS can alter neural drive (Dutta *et al*., 2015). Strengthened neural drive plays a particularly important role in increasing the rate of force develop-

	Sham	tDCS	*p*
Demographic Characteristics			
n	17	14	-
Age	37.1 +/- 13.1	33.2 +/- 11.23	0.38
Sex (% Female)	21.4	17.6	0.80
Psychological Measures			
Tiredness (1-7)	2.3 +/- 1.3	2.3 +/- 1.3	0.98
Average Sleep (hours per night)	6.8 +/- 1.5	7.1 +/- 0.9	0.54
Physiological Measures			
Blood Pressure (Systolic)	124.8 +/- 16	123.5 +/- 13.8	0.81
Blood Pressure (Diastolic)	78.2 +/- 10.5	77.9 +/- 7.5	0.93
Heart Rate	64 +/- 8.5	66.6 +/- 13.3	0.53
Exercise (days per week)	4.1 +/- 2.2	4.1 +/- 1.4	0.90
Baseline Performance			
Average RFD (arbitrary units)	1320.29	1275.62	0.26
Detectability of tDCS Status			
% Yes	78.5	76.5	0.89

Table 1. Subjects were separated into sham or tDCS groups. Values are represented as mean +/- SD unless otherwise noted. There were no significant differences ($p<0.05$) between the two groups.

ment (RFD) during a contraction (Aagaard *et al*., 2002). RFD, also known as explosive strength, is defined as the speed at which peak force is produced. It is a critical component in athletic proficiency, as the speed at which a muscle can generate force strongly correlates to how fast a motor action can be performed (Aagaard *et al*., 2002).

Although tDCS has been shown to improve motor performance across a wide variety of tasks and muscle groups, the current methods of administering tDCS are limited. For example, administration of tDCS is typically only available in a lab setting and requires a trained professional to administer treatment.

In the current study, the Halo Neurostimulation System was used to confirm and explore the effectiveness of tDCS in enhancing motor performance. The Halo Neurostimulation System was developed as part of a program to create a tDCS device that can be self-administered outside of a lab setting. It was designed to be easy to deploy, anatomically precise, and safe to use. The system used in the current study was composed of a wearable headset with a headphone form factor holding two saline-soaked electrodes over the conventional C3 and C4 EEG locations, connected to a small battery-powered neurostimulator controlled by a handheld Android device. In this particular study, the aim was to determine whether bihemispheric tDCS over M1 using the Halo device enhances motor performance in healthy adults. Bihemispheric tDCS was chosen because prior studies have indicated that bihemispheric tDCS magnifies behavioral effects by exciting one hemisphere while simultaneously inhibiting the other (Waters-Metenier *et al*., 2014). Bihemispheric tDCS also may prevent interhemispheric inhibition, i.e. overactivity in the dominant motor cortex that interferes with improvement of the non-dominant motor cortex.

Motor performance was tested using a lateral pinch force task (PF), during which subjects were required to squeeze a pinch gauge between their thumb and index finger as fast as possible with maximum voluntary force (isometric pinch). The task was performed before stimulation (baseline), during stimulation (online), and after stimulation (post-test). Subjects either received 2 mA of stimulation, or sham stimulation. As discussed previously, manipulation of cortical excitability via tDCS over M1 can improve neural drive to muscles, and enhanced neural drive strongly correlates to the rate of force development. Thus, we hypothesized that that subjects receiving 2 mA of stimulation would exhibit a significantly greater rate of force generation from baseline to online and offline tests, compared to those receiving sham stimulation.

METHODS

Participants

31 healthy right-handed subjects participated in the study. The handedness of subjects was evaluated using the Edinburgh Handedness Inventory. The sub-

jects were fluent in English and were medically and psychiatrically stable. Exclusion criteria for participation were as follows: (1) age above 75 or below 21 years; (2) left handed or ambidextrous (defined as a score of 175 or lower on the Edinburgh Handedness Inventory, which ranges from -350 to 350 with 350 corresponding to 100 percent right handed); (3) history of neurological or psychiatric illness; (4) history of drug or alcohol abuse; (5) history of brain tumor; (6) history of seizures within the last 5 years; (7) current usage of neuroactive medications; (8) Moderate or substantial hand or arm pain (defined as 5 or greater on a pain visual analogue scale ranging from 0-10 with 10 being maximally painful); (9) sickness (self-report); (10) tiredness (defined as 5 through 7, inclusive, on the 7-point Likert scale); (11) presence of an implanted medical device in the neurocranium or an active implantable medical device elsewhere in the body; (12) systolic blood pressure greater than or equal to 160 or diastolic blood pressure greater than or equal to 100; (13) currently pregnant or trying to become pregnant; (14) recent exposure (<28 days) to tDCS or transcranial magnetic stimulation (TMS); (15) enrollment in any other trial of a therapeutic investigational drug or device. Demographic characteristics of the included subjects are exhibited in Table 1. All participants gave written informed consent in accordance with applicable regulations and California Health and Safety Codes 24172 and 24173. The study was approved by MidLands Institutional Review Board. Participants were provided with an honorarium for participation.

Lateral Pinch Force Task

In order to assess motor performance, subjects completed a lateral isometric pinch force (PF) task before, during, and after stimulation. The pinch gauge utilized for the task was a Biometrics Precision Pinchmeter P200. The Pinchmeter was in the form of a disk with diameter 45mm and thickness 6 mm, and had a mass of 65 g. Force data were sampled at a rate of 7 Hz using a Biometrics DataLOG acquisition system and transmitted via Bluetooth to a personal computer. Rated load range was 0-22.5 kg and accuracy was defined by error less than 0.6% of rated load. During the lateral PF task, subjects were seated in front of a computer screen that displayed the force produced by each pinch. For each task, the lower left arm of the subject was rested horizontally anterior to the body on a table. During testing, subjects were instructed to hold the Pinchmeter in their left hand between the thumb pad and the middle phalanx of the index finger, the correct orientation for lateral pinch. During each pinch repetition, subjects were instructed to complete an isometric lateral pinch by pressing the Pinchmeter with maximal speed and force for 1-3 sec. The clinical trial assistant held one end of the Pinchmeter securely to ensure stability and consistency during each maximal pinch.

Procedure

This study employed a double-blind, sham-controlled experimental design to compare the effects of tDCS stimulation with that of sham stimulation over the primary motor cortex (M1) on a lateral isometric pinch force task. The experimental procedure is shown in Fig. 1. First, subjects completed an enrollment period where they were briefed on the trial and gave written informed consent to participate. The subjects were also evaluated via the Edinburgh Handedness Inventory and underwent baseline physiology tests. After enrollment, subjects entered the practice period, during which subjects completed a series of practice pinches. Subsequently, the Halo headset was assembled on the subject's head and subjects completed a baseline test that consisted of a series of pinches separated by fifteen seconds of rest. Depending on baseline performance, subjects were adaptively randomized to sham or 2 mA stimulation. A unique coded number was assigned to each subject from a preprogrammed list in order to randomize subjects. The clinical trial assistant did not know the meaning

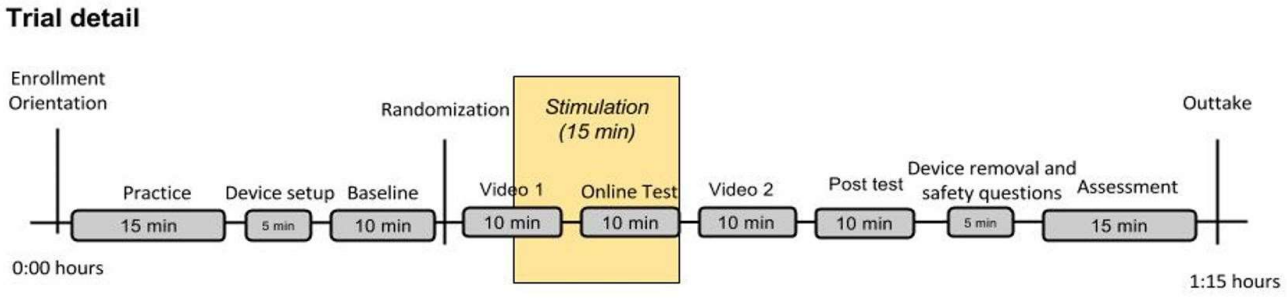

Figure 1. Experimental design.

of any coded number, and the behavior of the Halo Neurostimulation System was designed to appear identical in both the treatment and the sham cases. After the baseline test, subjects were allowed a rest during which a nature video with affectively neutral content was shown. The video was ten minutes total, and after five minutes of video, stimulation was begun. Subjects received fifteen total minutes of either sham or 2 mA stimulation. Five minutes into stimulation, subjects underwent an online training period identical to the baseline test. Once online training and stimulation ended, subjects were allowed a second video rest lasting ten minutes. After the video rest, subjects completed a post-test identical to both the baseline and online tests. Subsequently, the tDCS headset was removed and subjects answered a questionnaire designed to identify any adverse events. At the very end of the study, subjects underwent an assessment procedure during which physiological function (i.e. blood pressure and heart rate) was examined. Finally, subjects completed the outtake period, which included additional questions and compensation.

Transcranial direct current stimulation (tDCS)

tDCS was provided using the Halo Neurostimulation system. The electrodes were rectangular 6.4 x 4.4 cm sponges yielding a nominal contact region of 28 cm^2. Prior to tDCS administration, sponge contact surfaces were soaked in normal saline (0.9% NaCl). tDCS was administered as follows: anode electrode positioned over the right motor cortex (C4); cathode electrode positioned over the left motor cortex (C3). The intensity of stimulation was 2 mA. This stimulation was applied for 15 minutes in a single, contiguous session, which included a gradual current increase over 30 seconds at the beginning of the session and a gradual current decrease over 30 seconds at the end of the session. For the sham condition, tDCS was provided exactly as in the treatment group, except that stimulation was only delivered for the first 30 seconds of the training block. The current density at the stimulation electrodes was 0.071 mA/cm^2. This density is well below that which has been shown to cause brain tissue damage in animals in laboratory studies (25 mA/cm^2, McCreery *et al*., 1990) and is similar to the range of what has been used in prior published studies (0.0 - 0.066 mA/cm^2, Bastani & Jaberzadeh 2012). Comparable stimulation settings have been tested in multiple clinical trials and have proven to be safe in this subject population (Vines *et al*., 2008, Kantak *et al*., 2012).

Data Analysis

The primary outcome measure was rate of force development, defined as the maximum slope of the force-time curve over any given 10-millisecond time period while force was rising from 0 to its maximum value on any given pinch. Specifically, the dependent variable was the proportional change (with respect to a subject's baseline) in rate of force development measured during the training period. Values are shown in arbitrary force units provided by the Biometrics equipment. The primary endpoint hypothesized a difference in improvement — specifically, a difference in observed slope of force generation with respect to baseline — between sham and treatment groups. Data were analyzed using custom-written MATLAB routines. The threshold for significance in statistical comparisons was $p<0.05$. All data presented in figures are represented as mean +/- SEM.

RESULTS

The application of tDCS was safely completed in all subjects with no adverse effects. The increase in rate of force development (RFD) with respect to baseline, across the online test and the post-test, is shown in Fig. 2. Pinch events were first averaged within each subject and condition (i.e., online versus post), then averaged across subjects to yield the data shown. Since the study compared two independent subject groups containing a relatively small number of participants, and there was no assurance of a normal distribution, significance was determined using the Mann-Whitney U test (i.e., Wilcoxon rank-sum). At baseline, there was no significant difference in rate or force development between sham and tDCS groups (Table 1). For the online test, the rate of force development was significantly greater in the tDCS group than in the sham group ($p=0.009$). For the post-test, both groups demonstrated lower rates of force development relative to the online test. However, the group receiving stimulation still demonstrated a significantly higher rate of force development than the group receiving sham stimulation ($p=0.03$).

DISCUSSION

Previous studies have reported that tDCS over M1 can enhance motor performance across a wide spectrum of tasks. However, no study to date has investigated the effects of tDCS on rate of force development. Furthermore, tDCS research typically relies on a tDCS apparatus that must be administered by a researcher or medical professional in a lab setting. Thus, to our knowledge, the effect of tDCS on rate of force devel-

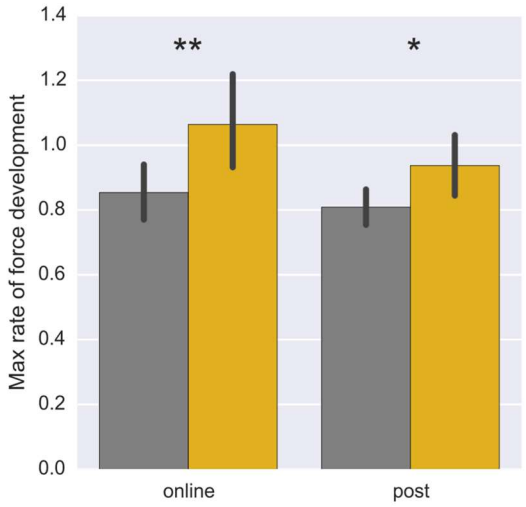

Figure 2. Transcranial direct current stimulation (tDCS) increases rate of force development (RFD) relative to baseline. Results showing the effect of tDCS delivered by the Halo Neurostimulation System on rate of force development (RFD) in the lateral pinch force (PF) task. The outcome measure, change in tDCS groups, respectively. The change in RFD is expressed in arbitrary units provided by the Biometrix equipment. The change in RFD with respect to baseline in the tDCS groups was significantly greater than that of the sham group during the online session (p=0.009) and the post-test (p=0.03).

opment has never been explored using an efficient, wearable device suitable for self-administration.

Therefore, the goal of the current study was to explore the effects of tDCS on rate of force development as part of a development program leading to a novel wearable device. In this double-blind, sham-controlled trial, it was found that 15 minutes of 2 mA bihemispheric tDCS administered via the Halo Neurostimulation System significantly enhanced rate of force development in healthy adults. The group receiving 2 mA tDCS exhibited significantly greater improvement in force generation relative to baseline in the PF task compared to the sham group both during stimulation and ten minutes after stimulation was complete. The fact that the rate of force development was significantly greater in the tDCS group compared to the sham group during the post-test exhibits the enduring effect of this stimulation. This finding is consistent with previous research indicating that the effects of tDCS can last for hours or even days after a stimulation session.

This study supports previous research showing that tDCS-induced modulations of cortical excitability in M1 can improve motor performance. The underlying mechanism of this occurrence is that increased cortical excitability in M1 increases motor unit recruitment, thereby increasing neural drive to the muscle (Dutta *et al*., 2015). Since neural drive is thought to be closely associated with rate of force development, the increased rate of force development found in our study is most likely due to increased cortical excitability in M1 induced by tDCS and not simply a result of training (Aagard *et al*., 2002).

The current study was conducted in a manner intended to improve upon previous tDCS research. For example, tDCS studies usually require 2 mA of stimulation for at least 20 minutes in order to reach significance. However, in the current study, significant results were achieved with just 15 minutes of 2 mA stimulation, which is advantageous in terms of time and energy efficiency. In addition, typical tDCS studies usually recruit a narrow age range (~18-30 years). In contrast, the current study had an expanded age range of 21-75 years, a range that more accurately represents the general population.

Although this study produced significant evidence that bihemispheric tDCS over M1 using the Halo device enhances rate of force development, some limitations must be considered. First, this study investigated the effect of tDCS on one specific hand strength task. Future studies should be conducted to determine whether the effects of tDCS administered via the Halo device would generalize to different tasks in other parts of the body. However, there is reason to believe that the improvements exhibited in this study would generalize to other motor tasks, as previous

studies have shown that tDCS can improve motor performance in both the arms and the lower limbs (Cogiamanian *et al*., 2007; Williams *et al*., 2013; Tanaka *et al*., 2009, van Asseldonk *et al*., 2015). Another limitation of this study is that only behavioral changes induced by tDCS were measured. Future work will be required to examine the neurophysiological changes associated with the behavioral gain observed in this study. However, given that previous studies have shown an augmentation of motor-evoked potentials (MEP) in M1 by tDCS, it is likely that electrophysiology measurements will correlate with the behavioral improvements seen in this study (Nitsche *et al*., 2005).

CONCLUSION

Previous work has indicated that bilateral tDCS over M1 is an effective method to improve motor performance in healthy individuals. The present study showed that bihemispheric tDCS applied over M1 using the Halo Neurostimulation System increases rate of force development in an isometric lateral pinch force task. This finding suggests that a convenient, wearable tDCS device could be a valuable resource for individuals seeking to improve explosive strength in daily life or in athletic training.

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