Bihemispheric Transcranial Direct Current Stimulation with Halo Neurostimulation System over Primary Motor Cortex Enhances Fine Motor Skills Learning in a Complex Hand Configuration Task

Halo Neuroscience

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ABSTRACT: Transcranial direct current stimulation (tDCS) is a noninvasive technique that modulates motor performance and learning. Previous research has shown that tDCS facilitates the learning of fine motor skills 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. Thus, the rationale of this study was to explore the effects of tDCS on motor skills learning 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 a Chord Configuration Task (CCT) in which the participant was required to reproduce a series of finger force patterns, akin to piano chords, as quickly and accurately as possible. tDCS delivered via the Halo Neurostimulation System was observed to facilitate motor skills learning, leading subsequently to faster and more synchronized execution. This study indicates that the Halo Neurostimulation System is an effective and safe method to enhance fine motor skills learning in healthy populations.

INTRODUCTION

The acquisition of fine motor skills plays a crucial role in facilitating both everyday tasks and specialized movements, such as playing an instrument or controlling a basketball. Motor skill learning is the process by which movements are executed more accurately and rapidly as a result of training. The primary motor cortex (M1) is thought to be a key brain area involved in the acquisition of fine motor skills (Vines et al., 2008).

Transcranial direct current stimulation (tDCS) is a noninvasive technique that modulates cortical excitability using electrical current and has been studied extensively 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 modulate the excitability of M1 (Nitsche et al., 2005). Previous studies have also indicated that motor skill acquisition is improved in both healthy and clinical populations when M1 is stimulated with anodal tDCS. Vines et al. (2008) and Cuypers et al. (2013) demonstrated that tDCS improves motor performance on the Finger Sequence Test (FST), in which the participant presses a sequence of keys on a keyboard as quickly as possible for a given interval of time. In addition, Hummel et al. (2009) found improved performance on the Jebsen-Taylor Test (JTT) after anodal tDCS over the left primary motor cortex in right-handed subjects. The Jebsen-Taylor Test is a seven-part test that evaluates the speed of hand functions used in daily activities. Subtests include writing, turning over cards, picking up small objects, using a spoon, stacking checkers, picking up cans, and moving cans. Of note, the greatest improvement seen in Hummel et al (2009) occurred in JTT subtests that evaluated fine motor control. In many motor skills studies, subjects maintained functional gains during, immediately after, and for multiple hours or days after stimulation. For example, Reis et al (2009) found that five consecutive days of anodal stimulation over M1 resulted in fine motor skills improvement that endured for three months after treatment. More recently, Waters-Metenier et al. (2014) found that 25

	Sham	tDCS	*p*
Demographic Characteristics			
n	17	14	-
Age	40 +/- 11.4	32.1 +/- 8.8	0.06
Handedness (Edinburgh)	332.4 +/- 41.2	305.8 +/- 46.9	0.11
Sex (% Female)	29	61.5	0.08
Psychological Measures			
Tiredness (1-7)	1.8 +/- 0.8	2.2 +/- 1.1	0.25
R-MMSE (0-15)	14.6 +/- 0.6	14.7 +/- 0.6	0.65
Physiological Measures			
Blood Pressure (Systolic)	133.7 +/- 15.1	119.3 +/- 10.1	0.005
Blood Pressure (Diastolic)	80.8 +/- 9.3	75.9 +/- 8.9	0.15
Heart Rate	74.4 +/- 9.9	71.6+/- 9.3	0.44
Hand/Arm Pain	0	0.2 +/- 0.6	0.26
Baseline Motor Performance			
Task Difficulty	12.4 +/- 4.7	13.4 +/- 4.6	0.59
Baseline CCT score	4.0 +/- 1.1	4.2 +/- 0.8	0.67
Detectability of tDCS Status			
% Yes	50	61.5	0.55

Table 1. Demographic and baseline characteristics. Figures given as mean +/- s.d.

minutes of bihemispheric tDCS at 2.0 mA improved both online (concurrent with stimulation) and offline (after stimulation) fine motor performance in a Chord Configuration Task (CCT), in which the participant creates a series of hand configurations or “chords” on a small keyboard at a given force as quickly as possible.

Although tDCS has been shown to effectively promote fine motor learning, the current methods of administering tDCS are limited. For example, administration of tDCS is typically only available in a lab setting and is generally not implemented efficiently. Furthermore, tDCS usually requires a trained professional to administer the treatment.

In this study, we used the Halo Neurostimulation System to confirm and explore the effectiveness of tDCS in facilitating motor learning. 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 is composed of a wearable headset containing two saline-soaked electrodes and a small battery-powered neurostimulator that is 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 fine motor skill learning in healthy adults. Bihemispheric tDCS was chosen because previous studies have indicated that Bihemispheric tDCS magnifies behavioral effects by exciting one hemisphere while simultaneously inhibiting the other (Vines et al. 2008). Bihemispheric tDCS may prevent interhemispheric inhibition, i.e. overactivity in the dominant motor cortex that interferes with improvement of the non-dominant motor cortex. Fine motor function was trained and tested using the Chord Configuration Task. In this task, subjects are required to reproduce a series of finger force patterns akin to piano chords as quickly as possible. The task was performed before stimulation (baseline), during stimulation (online), and after stimulation (offline). Subjects either received 1.4 mA of stimulation or sham stimulation. We hypothesized that subjects receiving 1.4 mA of stimulation would exhibit significantly greater improvement 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 subjects were fluent in English and were medically and psychiatrically stable. Exclusion criteria for participation were as follows: (1) age above 65 or below 21 years; (2) left handed or ambidextrous (defined as a score of 175 or less on the Edinburgh Handedness Inventory ranging from -350 to 350 with 350 corre-

sponding 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) expert or professional experience with a musical instrument; (9) A score of 12 or lower on a modified subset of questions from the Mini-Mental State Examination (MMSE) - subtest including 4 questions assessing orientation (1 pt each), one question assessing registration (3 pt), one question assessing attention and calculation (3pt), and one question assessing recall (5 pt) with a maximum total score of 15 points; (10) 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); (11) Long fingernails that would interfere with the subject's ability to perform the task; (12) sickness (self-report); (13) tiredness (defined as 5 through 7, inclusive, on the 7-point Likert scale); (14) presence of an implanted medical device in the neurocranium; (15) presence of an active implanted medical device; (16) systolic blood pressure greater than or equal to 160 or diastolic blood pressure greater than or equal to 100; (17) currently pregnant or trying to become pregnant; (18) recent exposure (<28 days) of tDCS or transcranial magnetic stimulation (TMS); (19) participation in previous Halo trials; (20) 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.

Participants were separated into sham or tDCS groups. Values shown in Table 1 are represented as mean +/- s.d. unless otherwise noted. There were no significant differences ($p<0.05$ by two-sample t-test) between the two groups, with the exception of systolic blood pressure.

Motor Task

In order to assess fine motor skill learning, subjects completed a Chord Configuration Task (CCT) before, during, and after stimulation. During the CCT, subjects were asked to press a series of piano chords on a small piano keyboard apparatus at a given force as quickly as possible with their non-dominant hand. The piano device was a MIDI keyboard (CME XKey) generating polyphonic aftertouch messages, calibrated with Halo software to yield consistent force results for each key. Only five keys on the keyboard were used. Participants were seated in front of the apparatus to yield a position similar to that used in piano playing. The configuration of each chord required subjects to press individual keys with varying amounts of force for each finger, and the specific keys to be pressed with a greater force varied from trial to trial. The task was adaptive during the calibration period, such that each subject received the difficulty level appropriate for his or her skill level. The chord was presented as vertical lines on a computer screen, such that the vertical position of each line was proportional to the force exerted by each finger on the respective key.

Procedure

This study employed a double-blind, sham-controlled experimental design to compare the effects of tDCS stimulation with sham stimulation over the primary motor cortex (M1) on a chord configuration task (CCT). 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. Subjects also underwent testing to assess basic cognitive function using a shortened version of the MMSE. In addition, blood pressure and pulse rate were recorded. After enrollment, subjects entered the 15-minute practice and

Figure 1. Experimental design.

calibration period, during which their left hand fine motor function was assessed using the CCT. In this initial period, the task difficulty was automatically adjusted proportional to the subject's ability to perform the task, by widening or shortening the acceptable range for the force of each keypress, and automatically selecting an appropriate difficulty-matched set of chords for training. This was completed via an algorithm whose goal was to bring each subject to a baseline score of approximately 4 seconds execution time per configuration.

Next, the Halo headset was assembled on the subject's head and a 15- minute baseline CCT testing period was completed. Subjects were randomized to sham or 1.4 mA stimulation using an adaptive randomization algorithm designed to minimize imbalance between baseline scores. A unique coded number was assigned to each subject from a preprogrammed list in order to deliver treatment according to this randomization. The clinical trial assistant did not know the meaning 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, the subjects underwent an online training period during which they received 25 total minutes of sham or 1.4 mA stimulation. The stimulation occurred concurrently with the first 25 minutes of the training block, which lasted 50 minutes total. The training block was broken up into 20 segments of 150 seconds each, consisting of 100 seconds performance time and 50 seconds of rest. In each segment, subjects performed 16 chords. Excess performance time, in cases where subjects completed the 16 chords in less than 100 seconds, was treated as additional rest time.

Once training ended, the tDCS headset was removed from the subjects' heads. Exactly five minutes after the end of the training period, subjects completed a post-test assessment, during which their left hand fine motor function was re-evaluated using the CCT. The chords used during this assessment period were identical to those used during the baseline period. At the very end of the study, subjects underwent an outtake procedure during which blood pressure, heart rate, and cognitive function were also re-assessed.

Transcranial direct current stimulation (tDCS)

tDCS was provided using the Halo Neurostimulation System. The electrode type selected for the study was a rectangular 6.4 x 4.4 cm sponge yielding a nominal contact region of 28cm2. 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), and cathode electrode positioned over the left motor cortex (C3). The intensity of stimulation was 1.4mA. This stimulation was applied for 25 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 0.05 mA/cm2. This density is well below that which has been shown to cause brain tissue damage (25mA/cm2, McCreery et al. 1990) and is within the range of what has been used in prior published studies (0.0-0.066mA/cm2, 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 performance time, defined as the interval from when a configuration (chord) was presented to the subject to when the chord was successfully performed. In accordance with the prespecified primary analysis, the observed data were fitted to a generalized estimating equation model (GEE) with compound symmetry correlation structure in order to assess the effect of treatment. Specifically, the dependent variable was the proportional change (with respect to a subject's baseline) in CCT score measured during the training period. The primary endpoint hypothesized a difference in improvement - specifically, a difference in observed slope of improvement with respect to baseline - between sham and treatment groups. Data were analyzed using custom-written MATLAB routines. The threshold for 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 observed. The percent improvement in performance time from baseline for both sham and treatment groups is shown in Fig. 2. The performance of both sham and stimulation groups improved gradually during stimulation and continued to improve for the rest of the 50-minute training block. However, the rate of learning in tDCS subjects was significantly greater than that of sham

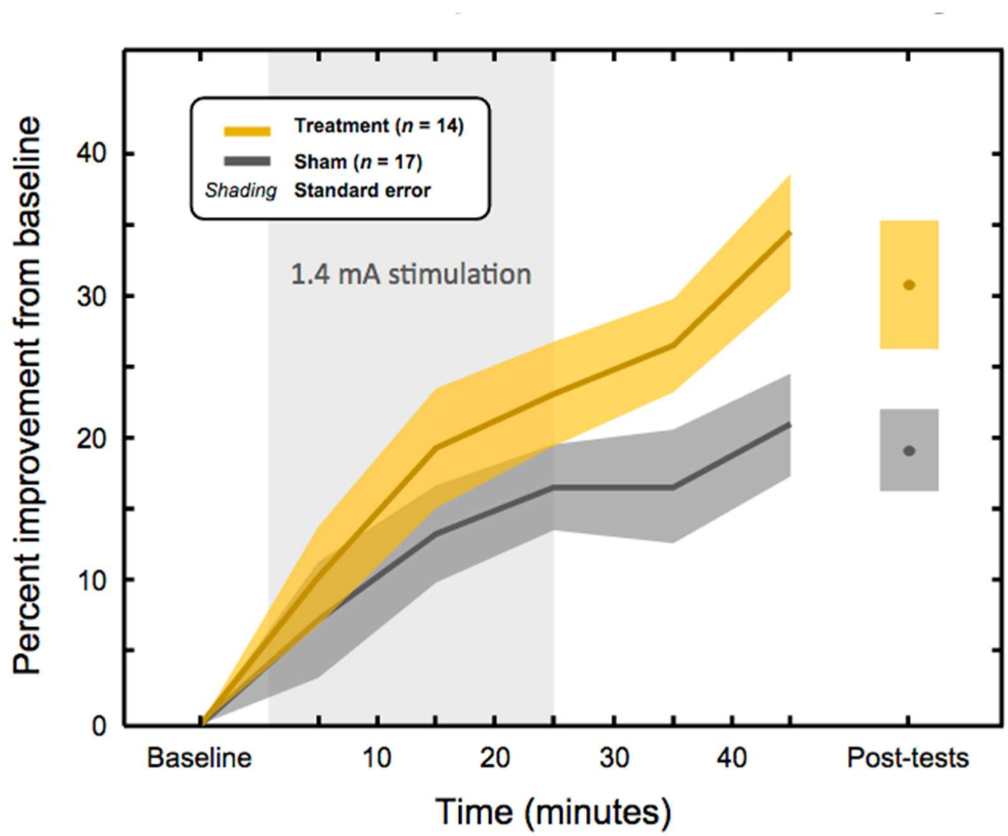

Figure 2. Halo Neurostimulation System increases fine motor skills learning. Shown here are results illustrating the effect of Halo tDCS on fine motor skills learning in the Chord Configuration Task (CCT). The outcome measure, finger pattern mean performance time, is represented as a plot of percent improvement from baseline as a function of time, with shading representing SEM. The rate of improvement (slope) of the group receiving 1.4 mA tDCS (yellow line) was significantly greater than that of the group receiving sham stimulation (grey line) ($p<0.028$). The 1.4 mA group also exhibited a significantly larger improvement during the post-test assessment compared to the sham group ($p< 0.039$).

subjects ($p=0.028$), as determined by a significant difference in slope between groups. Both groups also maintained gains during the post-stimulation test after training was completed. The tDCS group again exhibited significantly greater improvement than the sham group ($p=0.039$).

DISCUSSION

Previous studies have reported that bilateral tDCS over M1 enhances learning of fine motor skills in healthy adults. However, the type of tDCS required for this kind of research is typically inconvenient and inefficient, as it requires administration by a medical professional in a lab or hospital setting.

The goal of the current study was to explore the effects of tDCS on motor skill acquisition as part of a development program leading to a novel wearable device that offers efficient and anatomically precise neurostimulation outside of a medical setting. In this double-blind, sham-controlled trial, we found that 25 minutes of 1.4 mA bihemispheric tDCS administered via the Halo Neurostimulation System significantly enhances fine motor skill learning in healthy adults. The group receiving 1.4mA tDCS exhibited significantly greater improvement in the rate of motor skill learning relative to the sham group during stimulation. Subjects receiving 1.4 mA stimulation also exhibited significantly greater improvement in motor skill performance relative to sham during the post-stimulation test, which indicates the enduring effect of stimulation with the Halo device. 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 confirms the work of Waters-Metenier et al. (2014), who found that tDCS significantly improves fine motor performance in CCT over four days of stimulation. Our findings are consistent with these results, including the observation that significant improvements in CCT performance can be achieved within a single day. In addition to confirming findings of previous studies, the methods employed in the current study serve to strengthen and expand existing research. For example, while Waters-Metenier et al (2014) implemented 2mA of current, this study only required 1.4mA to achieve significant results, which is advantageous in terms of energy efficiency. In addition, Waters-Metenier et al. and other similar studies recruited subjects of a narrow age range (18-30 years). In contrast, the current study had an expanded age range of 21-65 years, a range that more accurately represents the general population.

Although this study produced strong evidence that bihemispheric tDCS over M1 using the Halo device enhances motor learning on a fine motor skills task, some limitations must be considered. First, this study investigated the effect of tDCS on a trained task only. Future studies should be conducted to determine whether the effects of tDCS administered via the Halo device would generalize to untrained tasks. However, there is reason to believe that the improvements exhibited in this study would generalize to untrained tasks, as previous studies have shown that tDCS improvements in fine motor skills learning can generalize to untrained hand configurations and finger sequences, as well as to the untrained hand (Waters-Metenier et al, 2014). 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 skills learning in healthy individuals. The present study showed that bihemispheric tDCS over M1 using the Halo Neurostimulation System increases learning in a task requiring the acquisition of fine hand motor skills. This finding suggests that a convenient, wearable tDCS device could be a valuable resource for individuals seeking to improve fine motor skills learning in daily life or in fields such as musical or athletic training.

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