

Original Reports

A Pilot Study of the Tolerability and Effects of High-Definition Transcranial Direct Current Stimulation (HD-tDCS) on Pain Perception

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Abstract: Several brain stimulation technologies are beginning to evidence promise as pain treatments. However, traditional versions of 1 specific technique, transcranial direct current stimulation (tDCS), stimulate broad regions of cortex with poor spatial precision. A new tDCS design, called high definition tDCS (HD-tDCS), allows for focal delivery of the charge to discrete regions of the cortex. We sought to preliminarily test the safety and tolerability of the HD-tDCS technique as well as to evaluate whether HD-tDCS over the motor cortex would decrease pain and sensory experience. Twenty-four healthy adult volunteers underwent quantitative sensory testing before and after 20 minutes of real (n = 13) or sham (n = 11) 2 mA HD-tDCS over the motor cortex. No adverse events occurred and no side effects were reported. Real HD-tDCS was associated with significantly decreased heat and cold sensory thresholds, decreased thermal wind-up pain, and a marginal analgesic effect for cold pain thresholds. No significant effects were observed for mechanical pain thresholds or heat pain thresholds. HD-tDCS appears well tolerated, and produced changes in underlying cortex that are associated with changes in pain perception. Future studies are warranted to investigate HD-tDCS in other applications, and to examine further its potential to affect pain perception.

Perspective: This article presents preliminary tolerability and efficacy data for a new focal brain stimulation technique called high definition transcranial direct current stimulation. This technique may have applications in the management of pain.

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Key words: tDCS, HD-tDCS, pain, TMS, MCS, electrical brain stimulation.

Implantable motor cortex stimulation, transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) are new brain stimulation methods that have shown at least preliminary promise as treatments for a variety of pain conditions.^{19,38,41}

The attractiveness of electrotherapy techniques includes the instant delivery of electricity (on demand, with no metabolic residue) to targeted brain regions. Unlike implantable motor cortex stimulation, which involves surgery, TMS and tDCS are minimally invasive

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receives funding from NIH and the Wallace H Coulter Foundation. The full amount of Dr. Borckardt's advisory income has never been more than 10% of his university salary. MUSC has 2 patent applications in Dr. George's name on combining TMS with MRI imaging. CUNY has 5 patent applications in Dr. Bikson's and Dr. Datta's names. Dr. Bikson and Dr. Datta are co-founders of Soterix Medical.

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methods and appear effective in the management of some forms of chronic pain.^{1,5,6,17,20,24,27,33,37,38,41} These technologies permit induction of changes in cortical excitability that may, in part, be related to changes in concentrations of glutamate and γ -Aminobutyric acid in the stimulated area.^{4,21} TMS applied over the motor cortex has been shown to significantly impact chronic neuropathic pain and experimentally induced pain.^{22,23,28-30} TMS over the prefrontal cortex has been shown to affect pain perception in neuropathic pain, experimentally induced pain, fibromyalgia, and postoperative pain.^{2,9-12,39} However, TMS is more complicated than tDCS to deliver and may be associated with more risks, particularly the potential for causing a seizure. Recent studies suggest that tDCS is more effective than sham stimulation at reducing pain in fibromyalgia and pain due to spinal cord injury^{17,20} and may be capable of modulating pain perception in central and laboratory-induced pain.^{6,17-19}

When managing pain with tDCS, the goal is to modulate activity in the areas of the brain that are involved in pain processing.³⁵ However, traditional tDCS techniques are spatially crude. Typically, large (5 × 7 cm) sponge electrodes are used to stimulate the human cortex and thus it is difficult to target smaller cortical targets. Sponge electrode position and size can modulate fractional current flow through specific brain regions,³⁴ but overall current distribution is widespread.¹⁴

High-definition transcranial direct current stimulation (HD-tDCS) is a new modification of traditional tDCS and uses arrays of specialized compact scalp electrodes to deliver current with no skin irritation and minimal discomfort.²⁵ Modeling studies can inform the configuration of these arrays to rationally guide current flow through the brain in an application- and subject-specific manner. For example, a 4 × 1 HD-tDCS deployment—where a central active electrode is surrounded by a ring of 4 return electrodes—is predicted to allow focally precise targeting of cortical regions with noninvasive electrical stimulation.¹⁴

The present study was conducted to evaluate the safety and tolerability of the HD-tDCS technique using the 4 × 1 ring deployment. Additionally, this single-blind, proof-of-concept, pilot study evaluated whether focal HD-tDCS over the motor cortex could decrease pain and sensory experience among healthy adult volunteers using standard quantitative sensory testing (QST) protocols. Finally, in order to understand the probable regions affected by the HD-tDCS arrangement used in this study, we carried out computer modeling using magnetic resonance imaging (MRI) scans.

Methods

Participants

Twenty-four healthy, medication-free, adult volunteers (18 female; 6 male; 3 African American; 1 Asian; 20 Caucasian) with a mean age of 26.58 (SD = 6.11; range 19 to 43) provided written informed consent to participate in this study. The study was approved by the Medical University of South Carolina (MUSC) Institutional Review

Board. Participants did not have depression, chronic pain, epilepsy, seizure history, or implanted medical devices. Two participants were nicotine-dependent smokers.

Quantitative Sensory Testing (QST)

Warm and Cool Sensory Threshold Assessment

Cutaneous warm and cool stimuli were delivered via the ATS thermode of the Medoc Pathway system (Medoc Advanced Medical Systems Ltd, Durham, NC) attached to the left volar forearm of each subject's left arm ~5 cm from the wrist. The thermode heated or cooled (randomly ordered) from 32°C at the rate of .25°C per second. Participants pressed a button to stop the thermode as soon as they detected any change in temperature. This procedure was repeated 10 times (5 warm; 5 cool). The interstimulus interval varied randomly between 3 and 10 seconds.

Hot and Cold Pain Threshold Assessment

Using the same location as above, the thermode again heated or cooled (randomly ordered) from 32°C at the rate of .5°C per second. Participants pressed a button to stop the thermode as soon as the temperature reached the level that they consider to be painful. This procedure was repeated 10 times (5 hot; 5 cold). The interstimulus interval was 20 seconds.

Mechanical Pain Threshold Assessment

The IITC Life Sciences (Woodland Hills, CA) Electric von Frey Anesthesiometer with rigid tips was used to apply pressure to the dorsal surface of the distal phalange of the *digitus minimus* of the left hand. Pressure was increased at the rate of 10 grams per second. Participants verbally indicated when the pressure reached the level that they consider to be painful. The pressure was recorded in grams. The procedure was repeated 5 times and the interstimulus interval was 20 seconds.

Thermal Wind-Up Pain Assessment

The CHEPS thermode from the Medoc Pathway System was used to deliver 20 brief (.75 second) suprathreshold thermal stimuli (individual heat pain threshold plus 1.5°C) to the left volar forearm of subjects at the rate of 1 stimulus every 1.5 seconds. During the 30 seconds of repeated stimulation, subjects continuously indicated their level of pain intensity using a dynamic computerized visual analogue scale (CVAS) controlled by the mouse. The CVAS recorded the position of the digital marker on the visual analogue scale each second. The mean of the pain ratings during the first 3 seconds and the last 3 seconds of the 30-second wind-up trial were examined to determine the amount of wind-up pain experienced by each participant.

Motor Cortex Localization and HD-tDCS Electrode Placement

A flexible plastic cap was placed on each participant's head and held in place with a chin strap. A Neuronetics TMS machine (Model 2100, Neuronetics Inc, Malvern, PA) with an iron-core, solid-state figure of 8 coil was

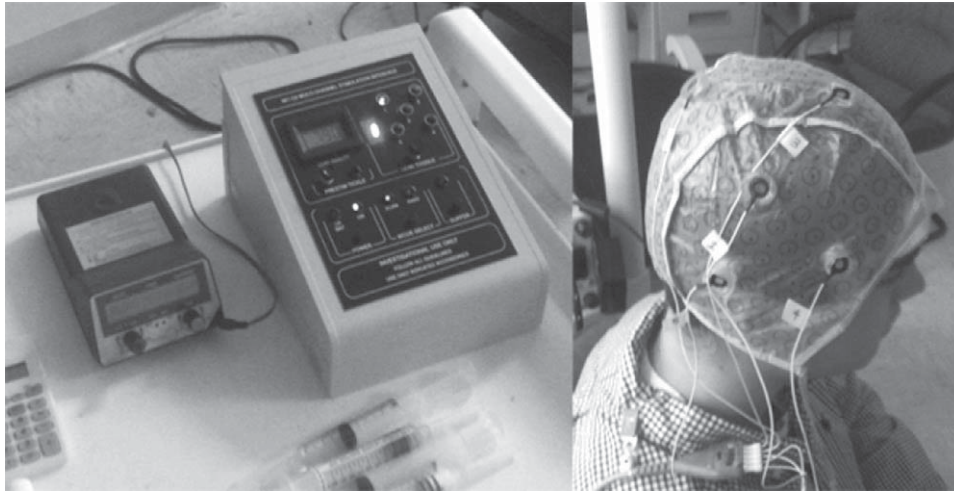


Figure 1. Photos of the HD-tDCS device and interface, and example of the electrode configuration used in the present study.

used to localize the cortical location that maximally caused movement of the abductor pollicis brevis (APB) muscle of the left hand. The TMS machine was set to 40% of maximal output with a frequency of .5 Hz and a systematic search strategy was implemented to localize the area of the motor strip associated with visual movement of the APB. The machine intensity was adjusted until APB movement was achieved and then localized. The coil location was marked with a nontoxic felt-tipped marker on the participant's cap. A computerized Parameter Estimation by Sequential Testing (PEST) algorithm was used to estimate resting motor threshold with visual thumb movement as the criteria.⁷ The PEST seed value was determined by the TMS administrator based on the best guess of the true threshold using information obtained during the localization process.⁷

HD-tDCS Methods and Stimulation Parameters

When conducting HD-tDCS, specially designed insets, electrodes, stimulation protocols, and conductive gels were used—appropriate instrumentation, electrode design, and protocols are considered important for HD-tDCS safety and comfort.³² The HD-tDCS anode casing³² was placed directly over the APB motor area located via TMS. Four cathode casings were placed equidistant from each other and from the anode (7 cm radius from anode). The electrode casings were first injected with 1 mL of a sterile solution containing 6% benzocaine and .2% benzethonium which was worked into the scalp using a cotton swab. After 10 minutes, 3 mL of Signa Gel (Parker Laboratories, NJ) was injected into the electrode casings. The electrodes were then placed into the gel solution inside the casings and held in place with the casing caps (Fig 1). Impedance values were examined for each of the 5 electrodes and were all verified to be <2 quality units. The HD-tDCS device was attached to a Phoresor-II Auto (Model PM850, Iomed, Salt Lake City, UT). Participants were then randomized to receive real or sham tDCS. For real HD-tDCS, the device was ramped to 2 mA and maintained this current for 20 minutes. For sham

HD-tDCS, the device was ramped to 2 mA, but after 30 seconds, was ramped back down to 0 mA and stayed off for the remainder of the 20 minutes.

Assessment of Subject Experience of HD-tDCS, Tolerability, and Mask Validity

During stimulation, participants rated the painfulness and unpleasantness of any scalp sensations using numeric rating scales (eg, 0 = no pain to 10 = worst pain imaginable). Ratings were collected at stimulation onset, 5 minutes, 10 minutes, 15 minutes, and during the last 30 seconds of stimulation). Further, verbal descriptors of all scalp sensations, pain-related or otherwise, were recorded as well as all adverse events associated with the study. At the end of the study, participants were asked to guess whether they received real or sham HD-tDCS. Further, they were asked to rate their confidence in their guess (0 = completely guessing to 10 = absolutely sure).

Procedures

All participants underwent phone screening for eligibility to participate and then completed the screening and informed consent procedures at the beginning of their single laboratory visit. Participants were seated comfortably in the MUSC Brain Stimulation Laboratory and underwent baseline QST procedures. Next, the HD-tDCS machine was set up and participants were randomized to condition (real or sham). Stimulation was started and participants were asked to describe any sensations they were experiencing as well as to rate the painfulness and unpleasantness of any scalp sensations (every 5 minutes during the 20-minute HD-tDCS session). After stimulation, participants underwent another round of QST. Participants were then asked to guess whether they received real or sham stimulation as well as their confidence in their guess. Participants were debriefed and compensated \$50.

Statistical Analyses

For mask integrity evaluation, chi-square tests were used to evaluate the number of participants correctly

guessing whether they received real versus sham HD-tDCS. Independent samples t-tests were used to evaluate guess confidence ratings as well as procedural scalp discomfort ratings. Mixed 2 (condition; real versus sham) \times 2 (time; pre- and post-HD-tDCS) models were run on the mean values from the thermal sensory, thermal pain threshold, and mechanical pain threshold tests while controlling for mean procedural pain ratings. Subject-level intercepts were included in the models as random effects. Main effects and interactions were examined for each model. For wind-up pain, the slopes of the visual analogue scale ratings were examined as a function of the condition \times time interaction.

Computational Model

In order to better understand the regions affected during this study, we carried out a computational model. For comparison, we showed the effects of conventional tDCS using the 5 \times 5-cm sponges.

MRI Derived High-Resolution Model

We developed an individualized finite element (FE) head model to compare the experimentally used HD-tDCS configuration with common conventional sponge pad tDCS. The head model was created from 1-mm³ resolution T1-weighted MRI scans of an adult male (MB) with no neurological pathologies. Using a combination of tools from the Functional MRI of the Brain Software Library (United Kingdom) and Simpleware (United Kingdom), the patient's head was segmented into compartments representing gray matter, white matter, cerebrospinal fluid, skull, scalp, eye region, muscle, air, and blood vessels (Custom Segmentation, Soterix Medical NY; Fig 2). The FE mesh generated from the segmentation masks was exported to COMSOL Multiphysics 3.5a (Burlington, MA) for computation of electric fields.¹⁵

Model Solution

We modeled the following electrode montages:

HD-tDCS. The anode center disc electrode was placed over the hand area of the right motor cortex. The four return cathode disc electrodes were placed equidistant from one another and from the anode similar to the experimental montage used in this study (Fig 2). This corresponded to a 7-cm center-to-center distance from the anode to each of the cathodes. All disc electrodes were 12 mm in diameter.

Conventional Pad tDCS. Two sponge-based pads (5 \times 5 cm) were placed at sites commonly used for tDCS to treat pain.⁴⁰ The active anode electrode was placed over the motor cortex, while the return cathode electrode was placed over the contralateral orbita.

Since the head model was directly derived from previously collected MRI data, it was limited to the anatomical sections collected. Thus, a synthetic neck and shoulder region was fused onto the existing segmented head.

Current densities corresponding to 2-mA total current were applied for each of the aforementioned stimulation configurations. The following isotropic electrical conductivities (in S/m) were assigned: gray matter, .276; white matter, .126; cerebrospinal fluid, 1.65; skull, .01; scalp, .465; eye

region, .4; air, 1e-15; synthetic region, .17; sponge, 1.4; and electrode, 5.8e7.^{14,15,40} The blood vessel compartment was assigned the same tissue property as that of scalp. The Laplace equation was solved and induced cortical electric field magnitude maps for the different electrode configurations were determined (Fig 2).

Results

HD-tDCS Brain Targeting Compared With Conventional tDCS, Modeling Prediction

FE method computational models predict brain current flow, and hence brain targeting, during electrical stimulation. High-resolution models yield predictions with sub-gyri specificity (Fig 2, top¹⁴). The high-definition 4 \times 1 ring montage (HD-tDCS) used in the present report was compared against a more conventional sponge-based tDCS montage (Fig 2). Consistent with previous predictions, HD-tDCS resulted in focal brain modulation with peak brain electric field under the center electrode, and brain modulation targeting restricted to within the ring perimeter (Fig 2A). In contrast, the conventional tDCS montage resulted in diffuse brain activation across the right temporal and bilateral frontal lobes, with peak brain electric fields clustered between (not under) the electrodes (Fig 2B). The electric field induced in the motor region, of interest in pain control, was comparable for the 2 montages.

These modeling studies suggest that the HD-tDCS montage can be used to target cortical motor regions, with comparable efficacy but manifestly improved specificity compared with conventional tDCS.

HD-tDCS Experience, Tolerability, and Mask Validity

Participants rated the scalp pain associated with real HD-tDCS as 1.98 (SD = 2.02) out of 10 on average while those receiving sham HD-tDCS rated their scalp pain as .18 (SD = .27). These means are both low considering the 11-point range of the numeric rating scale, but they were significantly different ($t[22] = 2.94, P = .008$). Participants receiving real tDCS rated the unpleasantness of the scalp sensations as 3.34 (SD = 2.44) out of 10 on average whereas those receiving sham rated the unpleasantness as .43 (SD = .49) on average ($t[22] = 3.88, P = .001$). The scalp painfulness and unpleasantness ratings associated with real tDCS decreased over time during stimulation (Figs 3 and 4). Despite the between-group differences in stimulation painfulness and unpleasantness, participants were not able to correctly guess whether they received real or sham stimulation at a rate better than chance ($X^2[1] = 2.10, P = .21, ns$). In the real stimulation group, 46% of participants guessed correctly ($X^2 = .004, P = .94, ns$) and in the sham group 18% guessed correctly ($X^2[1] = 2.23, P = .14, ns$). The average guess-confidence rating was 5.50 (SD = 3.10) in the real HD-tDCS group and 4.55 (SD = 2.16) in the sham group ($t[22] = .86, P = .399, ns$).

Qualitative descriptors of the scalp sensations during HD-tDCS included itchiness (21% of total sample),

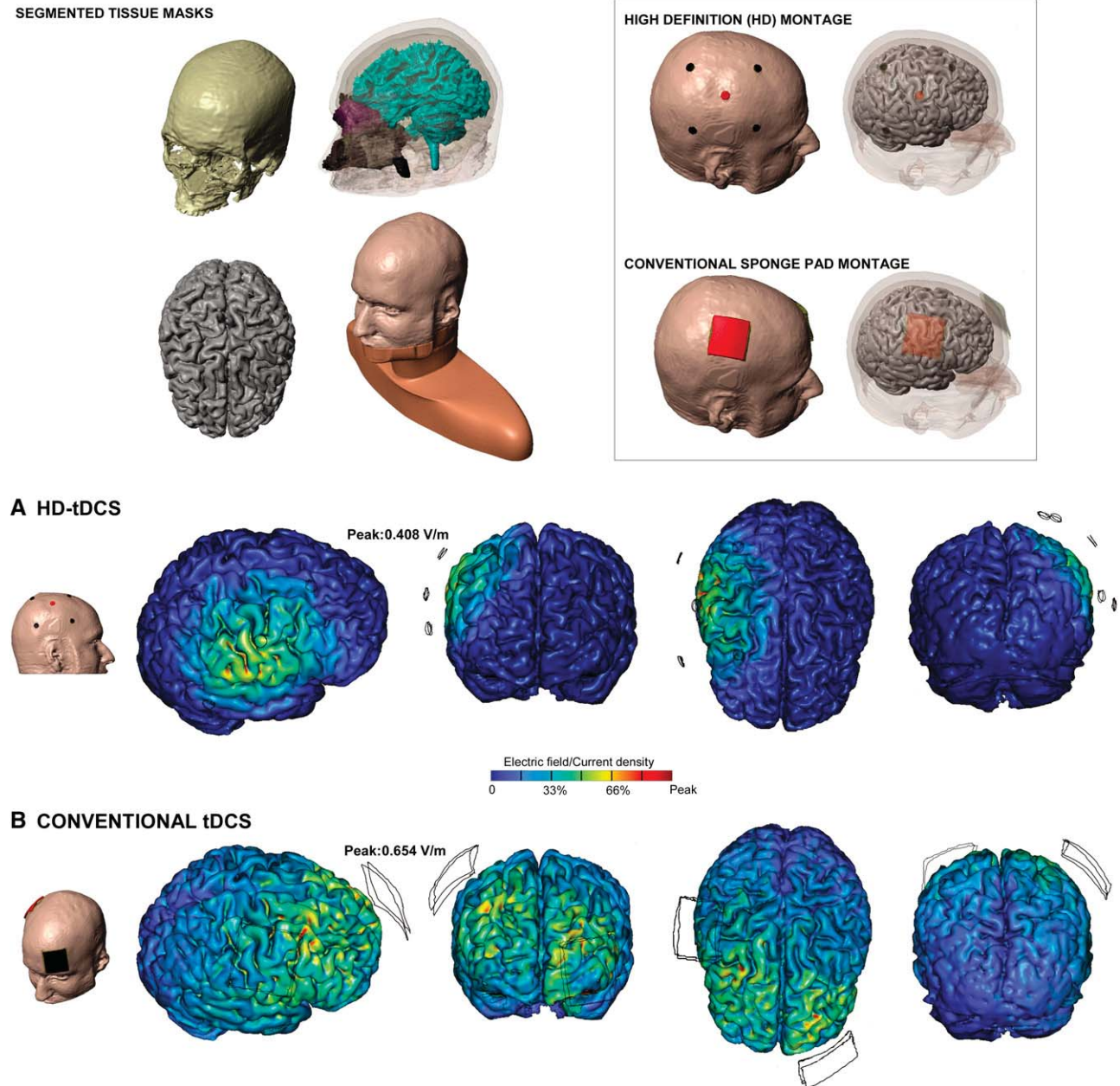


Figure 2. Computational models predict brain targeting by high-definition tDCS using the 4×1 montage compared with conventional tDCS using a bipolar sponge montage. **(Top left)** Sample segmentation masks of the high resolution individualized head model. **(Boxed Right Panel)** The high-definition 4×1 montage consisted of 1 anode, positioned over the motor region, surrounded by 4 cathodes at 7 cm radius (see comparable clinical Methods)—all the electrodes were high-definition mini electrodes. The conventional sponge montage used 1 anode centered over the motor region and 1 cathode over the contralateral supraorbital region—both electrodes were conventional sponge based. **(A)** High-definition tDCS resulted in brain current flow restricted to within the ring with peak brain activation under the center electrodes. **(B)** Conventional tDCS resulted in comparatively diffuse current flow with clustering of peaks between the electrodes (not under the electrodes).

tingling (21%), prickling (13%), pressure, stinging, uncomfortable, and warm (8% each). A total of 37 qualitative descriptors were offered by participants in the real HD-tDCS group and 17 from those in the sham group. Those offered by participants in the sham group were primarily during the 30 seconds of stimulation delivered before ramping the device back down to 0 mA for the remainder of the 20-minute session.

There were no adverse events, and no report of any poststimulation side effects.

Effects of HD-tDCS on Sensory and Pain Perception

Sensory Thresholds

There was a significant main effect for time (pre- to post-stimulation; $F[1,166] = 148.77, P < .0001$) but no main effect for condition (real versus sham stimulation; $F[1,26.4] = .04, P = .85, ns$) on heat sensory thresholds. The procedural pain covariate was not significant ($F[1,21] = 4.16, ns$). However, the time \times condition

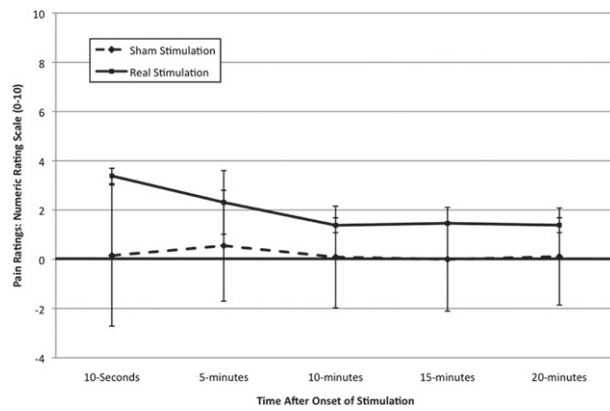


Figure 3. Procedural scalp pain associated with real and sham HD-tDCS during the 20-minute stimulation session.

interaction was significant ($F[1,166] = 5.34, P = .02$). Participants in the real stimulation group evidenced a .54°C increase (estimated marginal mean after controlling for procedural painfulness) in heat sensory threshold pre- to post-stimulation, relative to the sham group (Fig 5). For cold sensory thresholds, there was also a significant main effect for time ($F[1,165] = 50.82, P < .0001$) but not for condition ($F[1,29] = 1.64, P = .21, ns$), but the time \times condition interaction term was significant ($F[1,165] = 7.74, P = .006$). The procedural pain covariate was not significant ($F[1,21] = 3.17, ns$). Participants in the real stimulation group evidenced a .76°C decrease (estimated marginal mean after controlling for procedural painfulness) in cold sensory threshold pre- to post-stimulation relative to sham (Fig 6).

Thermal Pain Thresholds

A main effect for time was observed on heat pain thresholds ($F[1,260] = 64.94, P < .0001$), but no main effect was found for condition or for the time \times condition interaction term ($F[1,22.8] = .48, P = .49, ns; F[1,260] = .19, P = .66, ns$). The procedural pain covariate was not significant ($F[1,21] = .21, ns$). For cold pain thresholds, a significant main effect was found for time ($F[259] = 4.55, P = .03$) but not condition ($F[1,22.1] = 2.82, P = .11, ns$).

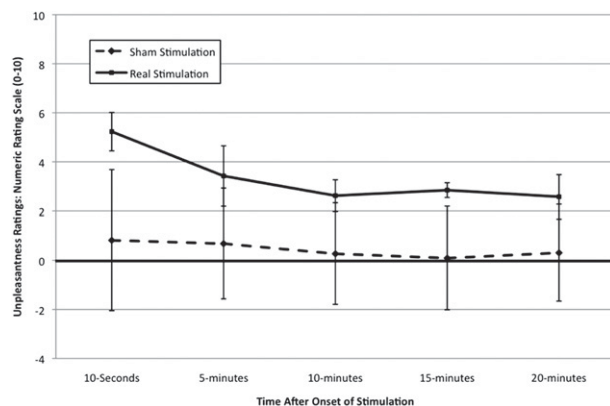


Figure 4. Procedural scalp sensation unpleasantness during real versus sham HD-tDCS during the 20-minute stimulation session.

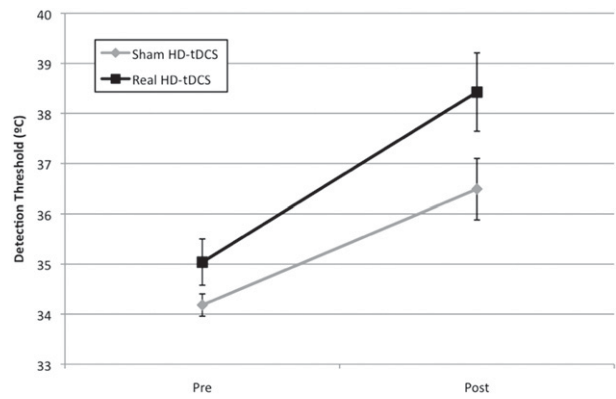


Figure 5. Mean (StdErr) heat sensory thresholds before and after real versus sham HD-tDCS (Time \times Condition Interaction $F[1,166] = 5.34, P = .02$).

Only a marginal effect was observed for the time \times condition interaction term ($F[1,259] = 3.18, P = .07$). The procedural pain covariate was not significant ($F[1,21] = .85, ns$). Participants who received real stimulation evidenced a .82°C decrease (estimated marginal mean after controlling for procedural painfulness) in cold pain threshold relative to sham (Fig 7).

Thermal Wind-Up Pain

A significant time (pre- to post-stimulation) \times condition (real versus sham stimulation) \times wind-up pain slope interaction was observed ($F[4,44] = 5.43, P = .001$). For those receiving real stimulation, the wind-up pain slope decreased by .25 CVAS pain-rating points-per-second (during the 30-second wind-up trial) following stimulation relative to baseline ($t[21.8] = 2.21, P = .036$). However, in the sham stimulation group, there was no change in wind-up pain slope pre- to post-stimulation ($t[30] = .52, P = .61, ns; Fig 8$).

Mechanical Pain Thresholds

A main effect for time was observed on mechanical pain thresholds ($F[1,262] = 18.92, P < .0001$) but an effect for condition was not found ($F[1,21.7] = .01, P = .98, ns$) nor for the time \times condition interaction ($F[1,262] = .92, P = .34, ns$).

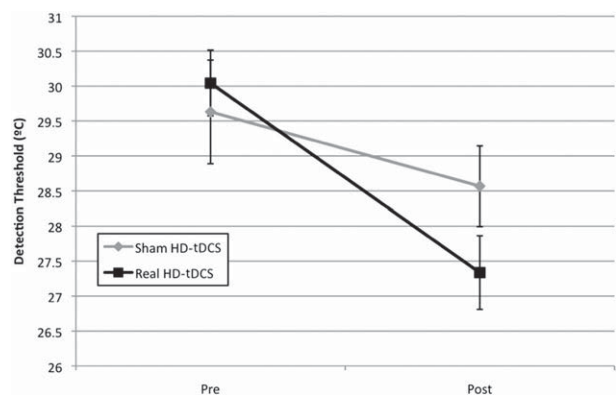


Figure 6. Mean (StdErr) cold sensory thresholds before and after real versus sham HD-tDCS stimulation (Time \times Condition Interaction $F[1,165] = 7.74, P = .006$).

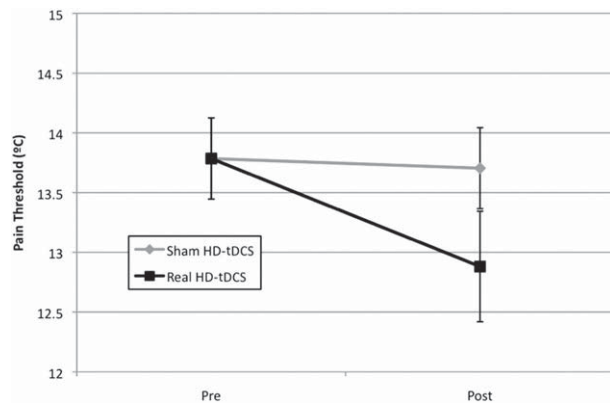


Figure 7. Mean (StdErr) cold pain threshold model-scores (controlling for baseline differences) before and after real versus sham HD-tDCS (Time \times Condition Interaction $F[1,259] = 3.18$, $P = .07$).

Discussion

Overall, these pilot findings support the tolerability of motor cortex HD-tDCS using the 4×1 deployment and specialized accessories. We emphasize that when conducting HD-tDCS, specially designed insets, electrodes, stimulation protocols, and conductive gels were used. As with any therapy, deviations from validated and prescribed equipment and protocols can introduce hazards.³² In the present study, no adverse events occurred and no significant side effects were reported that resulted in a need to discontinue stimulation. The scalp sensations most commonly associated with stimulation included itchiness, tingling, and prickling. The painfulness of the stimulation-induced scalp sensations was rated as 1.98 out of 10 on average in the real stimulation group. Further, these sensations decreased over time and the mean scalp pain rating during the last 30 seconds of the 20-minute real stimulation session was 1.39.

While there were differences in stimulation-induced scalp pain and unpleasantness, participants were unable to correctly guess whether they received real or sham stimulation, supporting the integrity of the blind. However, note that the rates of correct guessing, while not statistically significantly different, were 46% in the real HD-tDCS group and only 18% in the sham group. It is possible that with a slightly larger sample, this difference in correct guessing rates would become significant. Future studies should carefully attend to issues related to mask integrity.

In the present pilot, real HD-tDCS was associated with significantly decreased heat and cold sensory thresholds, decreased thermal wind-up pain, and a marginal analgesic effect for cold pain thresholds, all after controlling for procedural painfulness ratings. No significant effects were observed for mechanical pain thresholds or heat pain thresholds. Similar studies using a different technology (transcranial magnetic stimulation; TMS) suggest that stimulation of the motor cortex is associated with changes in heat and cold sensory thresholds as well as heat and cold pain thresholds.^{8,22,31} Using tDCS, Bachmann et al³ found that cathodal stimulation over the motor cortex significantly impacted cold sensory,

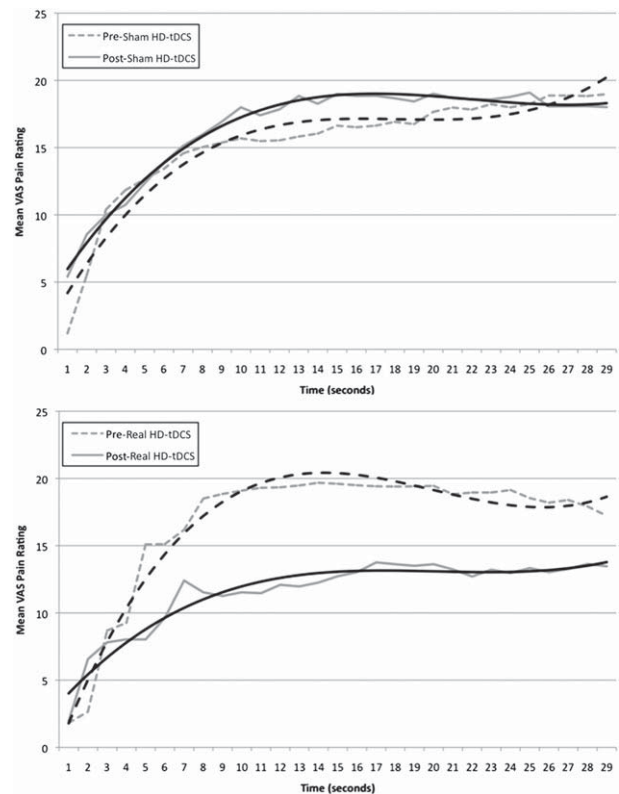


Figure 8. Mean continuous visual analogue scale (VAS) ratings and quadratic model estimates during 30-second thermal wind-up pain trials before and after real versus sham HD-tDCS. A significant time (pre- to post-stimulation) \times condition (real versus sham stimulation) \times wind-up pain slope interaction was observed ($F[4,44] = 5.43$, $P = .001$). A significant reduction in wind-up slope was detected pre- to post-real HD-tDCS ($t[21.8] = 2.21$, $P = .036$), but not sham ($t[30] = .52$, $P = .61$, ns).

mechanical sensory, and mechanical pain thresholds in the contralateral hand. Bachmann et al found no significant effects for cold pain thresholds, pressure pain thresholds, or wind-up pain. The simplest explanation for the divergence between these findings and those from the present study is the significant difference in the spatial profile of induced brain current flow (Fig 2). Craig et al¹³ found that the application of innocuous cold stimuli activates the human thermosensory cortex located in the contralateral insula. Painful heat and cold stimuli activated the contralateral anterior cingulate cortex, contralateral primary motor, and sensory cortex (M1: primary motor cortex/S1: primary sensory cortex), bilateral secondary sensory cortex (SII: secondary sensory cortex), and midinsular cortex, thalamus, and the vermis and paravermis of the cerebellum.^{16,36} Thus, the differing effects of HD-tDCS, TMS, and conventional tDCS seen on laboratory pain measures and nonpainful thermal and nociceptive thermal signals may be due, in part, to the transmission of signals related to perception via these different stimulus types and may occur through unique pathways.³ In addition, tDCS modulation of innocuous thermal thresholds may be more easily achieved than modulation of thermal pain thresholds, as thermal perception and distinction thresholds are lower than thermal pain thresholds.³

A range of electrotherapy technologies have been explored for the treatment of pain. The physiological

mechanisms of direct current therapy require further investigation, and the clinically optimal degree of focality/diffusivity remains to be established. However, note that HD-tDCS itself reflects a large constellation of potential array configurations, and the 4×1 ring deployment used in the present study can titrate depth, focality, and intensity depending upon the ring diameter. The variable control of spatial targeting provided with HD-tDCS arrays is thus a substrate to address questions of mechanisms and optimization. Invasive technologies, such as motor cortex stimulation, implant electrodes to achieve targeting—but any surgery is associated with complications and limitations. tDCS is a true neuromodulatory (sub-threshold) technique with a good safety and cost profile, but conventional tDCS technology results in diffuse brain modulation. HD-tDCS is a new electrotherapy modality proposed to be the first noninvasive and targeted neuromodulatory technique.¹⁴

Note that the HD electrodes used in this study (including specially designed insets and gels) were specifically optimized to allow safe stimulation under the dosages tested here and because of precise control on contact conditions (in contrast to conventional sponge-pad tDCS), stimulation can be applied reliably. We consider proper control of stimulation protocols (electrode design, position/prep, tDCS dose) a more robust method to prevent injury since subject sensation is neither sufficient nor necessary for skin burns. Still, if someone were to use a different (more potent) topical anesthetic this might: 1) change the contact conditions leading to potential damage; and 2) if the skin were truly numb, mask hazards.

While the analgesic nature of the present pilot study findings are encouraging, more work is needed to

further establish the potential clinical benefit of HD-tDCS for pain as well as to optimize dosing and cortical targeting strategies. While some statistically significant effects were observed, the clinical applicability of this technology still needs to be established given that the changes associated with HD-tDCS were small in this study. However, the clinical impact of HD-tDCS might be well boosted by repeated sessions (as is typically seen in clinical studies). Indeed, the flexibility and targeting advantages of HD-tDCS, where brain current flow can be controlled by the configuration of scalp electrodes, warrants further investigation of HD-tDCS in other experimental and clinical studies. Note that the results of this pilot trial might have been different if electrode polarity was reversed (ie, cathodal stimulation), because the type of circuits recruited by cortical stimulation depends on the relationship between fiber orientation and electrode polarity.^{26,29} The present study did not investigate the role of cathodal-center 4×1 HD-tDCS, wherein the dominant polarization under the center electrode would have changed from somatic depolarization (center anode) to somatic hyperpolarization (center cathode).

In summary, these pilot findings support the tolerability of motor cortex HD-tDCS using the 4×1 deployment and specialized accessories. Real HD-tDCS was associated with significantly decreased heat and cold sensory thresholds, decreased thermal wind-up pain, and a marginal analgesic effect for cold pain thresholds, all after controlling for procedural painfulness ratings. No significant effects were observed for mechanical pain thresholds or heat pain thresholds. More studies of the potential effects of HD-tDCS on laboratory and clinical pain seem warranted.

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