Received: June 11, 2012 Revised: October 10, 2012 Accepted: October 31, 2012

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12009

Modulation of Cold Pain Perception by Transcranial Direct Current Stimulation in Healthy Individuals

Ali Zandieh, MD, MPH*, Seyed Ehsan Parhizgar, MD‡§, Mohammad Fakhri, MD*, Mohammad Taghvaei, MD, MPH‡, Shahin Miri, MD‡, Alireza Shahbabaie, MS†, Sadaf Esteghamati, MD*, Hamed Ekhtiari, MD†§

Objectives: The aim of the current study was to evaluate the effect of transcranial direct current stimulation (tDCS) on cold pain perception in healthy individuals.

Methods: Anodal, cathodal (2 mA), or sham tDCSs were applied on the primary motor cortex of 22 healthy subjects in a random order. A cold pressor test was performed ten minutes after initiation of stimulation. Pain threshold and tolerance were defined as time latencies to the onset of pain perception and to the withdrawal from cold stimulus, respectively. Furthermore, pain intensity (on a scale from 0 to 10) was rated at tolerance.

Results: Time latencies to pain threshold and tolerance were altered by the type of stimulation ($p < 0.05$). Pairwise *post hoc* analysis revealed that anodal tDCS led to increment in pain threshold and tolerance compared with sham stimulation (13.3 $\pm$ 7.4 vs. 10.9 $\pm$ 6.0 sec for the comparison of pain threshold and 54.6 $\pm$ 26.0 vs. 45.3 $\pm$ 17.9 for the comparison of pain tolerance following anodal and sham stimulations, respectively, $p < 0.05$ for both comparisons). However, cathodal stimulation did not alter pain perception in comparison to anodal and sham stimulations ($p > 0.05$). Furthermore, pain intensity score at tolerance was not significantly affected by the type of stimulation ($p > 0.05$).

Conclusion: Anodal stimulation of the primary motor area can be utilized to alleviate cold pain perception in healthy individuals.

Keywords: Healthy subjects, pain, primary motor cortex, transcranial direct current stimulation

Conflict of Interest: The authors declare no conflicts of interests.

INTRODUCTION

Cortical excitability can be influenced by a variety of invasive and noninvasive techniques. In this regard, transcranial direct current stimulation (tDCS), as a noninvasive technique, delivers a current flow through electrodes and reversibly alters the excitability of cortical neurons (1,2). It has been shown that the current intensity is maximal in cortical areas directly under the electrodes and rapidly decreases at sites more distant from the electrodes (3–5). It is suggested that tDCS confers most of its effects through modulation of cortical excitability in those areas directly covered by electrodes (5). However, other areas also may be stimulated. For instance, placement of the electrode over the primary motor area also may alter the neuronal excitability of the premotor area and postcentral gyrus in addition to the primary motor area (6). Moreover, the effects of tDCS also depend on duration, polarity, and intensity of the stimulation (7,8). In this respect, anodal stimulation enhances and cathodal stimulation diminishes the neuronal excitability, possibly through modulation of membrane-resting potential (7,9,10). Furthermore, distinct groups of local cortical nerve cells are influenced by anodal and cathodal stimulations of the same brain area (11,12).

Many prior studies have evaluated the effects of tDCS on sensory and pain perception. For instance, it has been shown that tDCS influences visual and tactile perception, as well as cognitive function (13–15). Furthermore, Grundmann et al. have found that stimulation of the primary sensory cortex mediates somatosensory perception (16). Anticonvulsant effects also have been reported for tDCS in a rat model of focal epilepsy (17). A review of previous studies shows that tDCS over the motor cortex ameliorates pain in patients with chronic pain syndromes such as traumatic spinal cord injury, fibromyalgia, and cancer pain (18–21). However, evidence to support the impact of tDCS on acute thermal pain perception is limited, and the role of current stimulation in somatosensory input

Address correspondence to: Hamed Ekhtiari, MD, Institute for Cognitive Sciences Studies (ICSS), No. 18, Pezeshkpour Alley, Vali-asr Avenue, P.O. Box 15948, Tehran, Iran. Email: h_ekhtiari@razi.tums.ac.ir; h.ekhtiari@gmail.com

* Iranian Center of Neurological Research, Tehran University of Medical Sciences, Tehran, Iran;
† Institute for Cognitive Sciences Studies (ICSS), Tehran, Iran;
‡ Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran; and
§ Neurocognitive Laboratory, Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/bw/submit.asp?ref=1094-7159&site=1

remains to be fully elucidated. A recent study has shown that although anodal stimulation decreases heat and cold sensory thresholds, it does not affect heat pain threshold and just barely influences the threshold of cold pain perception (22). Another study has revealed that neither anodal nor cathodal tDCS significantly changes variables related to somatosensory and pain perception (23). On the contrary, Bachmann et al. have reported reduced sensitivity of nerve fibers to somatosensory inputs following cathodal stimulation of the primary motor area (24).

Conflicting data in the association of cortical stimulation and pain perception necessitate the importance of performing further studies in this area of research. The current study evaluates the modulatory effects of anodal, cathodal, and sham stimulations on pain threshold and tolerance in healthy individuals. Furthermore, we compared pain intensity scores at tolerance.

METHODS

Subjects

A total number of 22 healthy subjects (mean age ± standard deviation of 27.9 ± 4.8 years; 12 men, 10 women) were enrolled. All subjects were right-handed according to the Edinburgh handedness inventory, and none of them were under any regular medical treatment (25). Furthermore, the subjects with chronic pain and neurologic or psychiatric disorders, as well as those who received analgesic medications within the past 24 hours, were not included. Furthermore, the subjects with a history of substance abuse, dependence, brain surgery, tumor, or intracranial metal implantation were excluded. All subjects were able to understand and follow the protocol of the current study and gave written informed consent before study commencement. Furthermore, the study was performed in agreement with the Helsinki Declaration and was conducted in accordance with considerations, recommended by the local ethics review committee of Tehran University of Medical Sciences.

tDCS

Direct current stimulation was applied using a saline-soaked pair of surface sponge electrodes with a surface area of 35 cm^2. Electrical current was developed by a constant current stimulator having a maximum output intensity of 10 mA. Anodal, cathodal, or sham stimulations were delivered in a random order separated by one-week intervals. For stimulation of the left primary motor cortex, the active electrode was placed over the C3 electrode position on the scalp due to the 10–20 electroencephalogram system, and the reference electrode was placed over the contralateral supraorbital area. In anodal and cathodal stimulations, an electrical stimulus with a current intensity of 2 mA was applied for a maximum of 15 min. For sham stimulation, the current flow increased up to 1 mA and terminated after 20 sec in order to mimic the initial tingling sensation of the electrical current.

Cold Pressor Test

A cold pressor test was performed in line with guidelines recommended in prior studies (26–28). The experiment was conducted in a quiet and convenient room (with a temperature of 22 ± 2°C) without any auditory or visual distractions. We used two tanks containing 20 L of water continuously stirred by a pump to prevent inhomogeneity in the water temperature. Both tanks were equipped with a digital timer and an internal thermostat to maintain the water temperature at the reference level. Ten minutes after the onset of tDCS, the subjects were instructed to place their right hand up to the elbow for one minute in the first water tank, which was at 35 (±0.5)°C. Then, the subjects were asked to immediately immerse their right hand up to the elbow in the second tank, which was maintained at a temperature of 3 (±0.5)°C and, simultaneously, a stopwatch was activated. The time latency to the initiation of pain sensation was recorded as the pain threshold. In addition, the time point, in which the subjects withdrew their hands from the cold pressor apparatus, was determined as a measure of pain tolerance (in seconds). Pain intensity was rated at tolerance, using an 11-point scale ranging from 0 (no pain) to 10 (extremely severe pain).

Statistical Analyses

All analyses were conducted using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA). Considering that some variables were not normally distributed, we used the Friedman test for studying the effects of anodal, cathodal, and sham stimulations on latencies to threshold and tolerance and pain intensity score. Significant results were further analyzed with the Wilcoxon *post hoc* test. After correcting by the Bonferroni method, a p-value <0.05 was considered statistically significant.

RESULTS

All 22 enrolled subjects tolerated the procedures well, and no adverse effects were reported. A tingling sensation was perceived by 18 subjects at the beginning of the experiment.

Table 1 summarizes the effects of different kinds of stimulations on latencies to cold pain threshold and tolerance, as well as pain intensity score. In contrast to pain intensity score, which was not modulated by the type of stimulation ($p > 0.05$), time latencies to threshold and tolerance were influenced by different kinds of stimulations ($p < 0.05$). The Wilcoxon *post hoc* test revealed that anodal tDCS increased the threshold for pain perception compared with sham stimulation (13.3 ± 7.4 vs. 10.9 ± 6.0 sec, $p < 0.05$). However, the threshold after cathodal stimulation was not significantly different from anodal and sham stimulations ($p > 0.05$). Similarly, pairwise comparison revealed that anodal stimulation increased the tolerance of the subjects for pain perception in comparison to sham tDCS (54.6 ± 26.0 and 45.3 ± 17.9 sec, $p < 0.05$). Finally, cathodal tDCS did not significantly alter the time latency to pain tolerance ($p > 0.05$).

Table 1. Time Latencies of Cold Pain Threshold and Tolerance After Sham, Cathodal, or Anodal Stimulations.

	Sham stimulation	Cathodal stimulation	Anodal stimulation
Latency to threshold (sec)	10.9 ± 6.0	11.3 ± 6.4	13.3 ± 7.4*
Latency to tolerance (sec)	45.3 ± 17.9	46.9 ± 19.8	54.6 ± 26.0*
Pain intensity score (unites)	6.57 ± 1.7	7.09 ± 1.6	7.32 ± 1.8

Data are presented as mean ± standard deviation.
*$p < 0.05$ for the comparisons made by the Friedman test.

DISCUSSION

Results of the current study demonstrate that anodal tDCS of the primary motor area increases cold pain threshold and tolerance in healthy individuals. In contrast, no significant effect was observed for cathodal tDCS. Our findings extend the evidence regarding the role of anodal stimulation in pain perception to the normal baseline neuronal activity.

Pain perception in the human brain results from a complicated and distributed mechanism. In contrast to other sensory systems, various arrays of functionally distinct regions are involved in pain processing (29). This phenomenon may explain the preservation of pain perception in the subjects with extensive cerebral cortical lesions (29). In this regard, we found that anodal stimulation of the primary motor area leads to increment in time latencies to pain threshold and tolerance. In line with our findings, a review of previous studies shows that among different regions of the brain, transcranial stimulation of the motor cortex is the most common approach for alleviation of chronic pain (30–32).

Although electrode placement over the primary motor area is most effective on the motor cortex, some other areas also may be stimulated (e.g., postcentral gyrus) (6). Using neuroimaging techniques, Zheng et al. have reported that placing the electrode over the primary motor cortex would result in an altered activation of neurons in the ipsilateral premotor region and less strongly in the contralateral motor and premotor regions in addition to the directly targeted area (i.e., primary motor cortex) (33). It is suggested that besides functional interactions between various areas of the brain, inhomogeneities in electrical conveyance of the skull, cerebrospinal fluid, and brain tissue also may play roles in the pattern of the spatial distribution of current flow and neuronal activation (9). Thus, it may be conceivable to say that some of the effects observed following motor cortical area stimulation may be related to the alterations in the neuronal excitability of other regions. In line with many prior studies, we found that anodal and cathodal stimulations differ with respect to their effects on sensory perception. In this regard, Antal et al. reported diminished pain perception following cathodal (but not anodal) stimulation of somatosensory cortex (34). Thus, the antinociceptive effects, which we observed in the current study following anodal stimulation of the primary motor area, are unlikely modulated by somatosensory cortex. However, because various brain regions are involved in pain perception and tDCS alters neuronal excitability in a complex spatial pattern, it is difficult to reveal the underlying pathophysiologic pathways that relate cortical stimulation of the primary motor area to pain perception.

In the current study, the subjects also were asked to rate the intensity of pain at tolerance. We found that although anodal stimulation compared with either sham or cathodal stimulation prolongs tolerance, there is no significant difference in the subjective scores of pain. However, one earlier study has shown reduction in subjective pain scores in healthy individuals following tDCS (35). Similarly, another study reported that subjective measures of pain perception decreased in patients with a traumatic spinal cord injury after receiving stimulations (18). One possible reason for this discrepancy is that we measured pain intensity at tolerance. It may be reasonable to suggest that because the length of time for the tolerance to pain was prolonged with tDCS, therefore, such subjective scores for pain intensity showed no significant difference.

As we stated earlier, one possible negative aspect of tDCS is that it modulates cortical excitability in a relatively complex spatial pattern. It has been shown that reducing the size of the stimulating electrode may help to focus the distribution of current flow and excitability changes (5). However, in the current study, similar to most prior studies, we used electrodes with a surface area of 35 cm^2 in order to increase the comparability of our findings (36–38).

Different invasive (e.g., epidural motor cortex stimulation) and noninvasive procedures (e.g., transcranial magnetic stimulation and tDCS) have been introduced for pain alleviation (39). Although a meta-analysis has showed the higher efficiency of invasive procedures for pain control (40), the current study has the advantage of using a widely used noninvasive procedure, which costs less and also is easy to administer. Furthermore, for procedures other than tDCS, there are a greater number of parameters that vary across different studies (39). This phenomenon precludes a formal direct comparison of those studies. Moreover, it should be noted that tDCS is a safe technique with few discomforts. Another advantage of this study is that we employed a cold pressor test, which is widely used for cold sensory and pain perception (26–28,41). We used a thermostat to keep the water temperature constant during the experiment. Furthermore, the room temperature was maintained at a constant level in order to reduce its influence on the measures of pain perception.

In conclusion, the current study suggests that, in contrast to cathodal stimulation, anodal tDCS increases time latencies for cold pain threshold and tolerance. We found that abnormal neuronal activity is not needed for tDCS to exert its effects on pain perception. Furthermore, tDCS does not alter subjective scores of pain at tolerance. Our findings may have therapeutic relevance for some specific diseases such as trauma-induced cold intolerance (24,42,43). Because of vast ambiguities regarding pain perception and tDCS influence on the nervous system, further studies in this line are required to understand the underlying mechanisms that lead to pain reduction following anodal stimulation.

Acknowledgment

This study was supported with grants from Institute for Cognitive Science Studies (ICSS) and Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences (TUMS).

Authorship Statements

Drs. Zandieh and Parhizgar conceived, designed, and conducted the study, participated in the acquisition and interpretation of data, and Dr Zandieh wrote the primary draft of the manuscript. Dr. Taghvaei participated in the acquisition and interpretation of data. Drs. Miri and Esteghamati helped draft the manuscript and participated in the acquisition of data. Mr. Shahbabaie participated in the study design and acquisition of data. Dr. Ekhtiari designed and supervised the study process. All authors read and approved the final manuscript.

How to Cite this Article:

Zandieh A., Parhizgar S.E., Fakhri M., Taghvaei M., Miri S., Shahbabaie A., Esteghamati S., Ekhtiari H. 2012. Modulation of Cold Pain Perception by Transcranial Direct Current Stimulation in Healthy Individuals. Neuromodulation 2012; e-pub ahead of print. DOI: 10.1111/ner.12009

REFERENCES

1. Been G, Ngo TT, Miller SM, Fitzgerald PB. The use of tDCS and CVS as methods of non-invasive brain stimulation. *Brain Res Rev* 2007;56:346–361.
2. Wassermann EM, Grafman J. Recharging cognition with DC brain polarization. *Trends Cogn Sci* 2005;9:503–505.
3. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. *Clin Neurophysiol* 2006;117:1623–1629.
4. Rush S, Driscoll DA. Current distribution in the brain from surface electrodes. *Anesth Analg* 1968;47:717–723.
5. Nitsche MA, Doemkes S, Karakose T et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2007;97:3109–3117.
6. Matsunaga K, Nitsche MA, Tsuji S, Rothwell JC. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clin Neurophysiol* 2004;115:456–460.
7. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527 (Pt 3):633–639.
8. Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. *Suppl Clin Neurophysiol* 2003;56:255–276.
9. Lang N, Siebner HR, Ward NS et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J Neurosci* 2005;22:495–504.
10. Nitsche MA, Seeber A, Frommann K et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol* 2005;568:291–303.
11. Manola L, Holsheimer J. Motor cortex stimulation: role of computer modeling. *Acta Neurochir Suppl* 2007;97:497–503.
12. Manola L, Holsheimer J, Veltink P, Buitenweg JR. Anodal vs cathodal stimulation of motor cortex: a modeling study. *Clin Neurophysiol* 2007;118:464–474.
13. Antal A, Nitsche MA, Paulus W. Transcranial direct current stimulation and the visual cortex. *Brain Res Bull* 2006;68:459–463.
14. Rogalewski A, Breitenstein C, Nitsche MA, Paulus W, Knecht S. Transcranial direct current stimulation disrupts tactile perception. *Eur J Neurosci* 2004;20:313–316.
15. Boggio PS, Ferrucci R, Rigonatti SP et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol Sci* 2006;249:31–38.
16. Grundmann L, Rolke R, Nitsche MA et al. Effects of transcranial direct current stimulation of the primary sensory cortex on somatosensory perception. *Brain Stimul* 2011;4:253–260.
17. Liebetanz D, Klinker F, Hering D et al. Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. *Epilepsia* 2006;47:1216–1224.
18. Fregni F, Boggio PS, Lima MC et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 2006;122:197–209.
19. Fregni F, Gimenes R, Valle AC et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum* 2006;54:3988–3998.
20. Silva G, Miksad R, Freedman SD et al. Treatment of cancer pain with noninvasive brain stimulation. *J Pain Symptom Manage* 2007;34:342–345.
21. Bittar RG, Kar-Purkayastha I, Owen SL et al. Deep brain stimulation for pain relief: a meta-analysis. *J Clin Neurosci* 2005;12:515–519.
22. Borckardt JJ, Bikson M, Frohman H et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. *J Pain* 2012;13:112–120.
23. Jurgens TP, Schulte A, Klein T, May A. Transcranial direct current stimulation does neither modulate results of a quantitative sensory testing protocol nor ratings of suprathreshold heat stimuli in healthy volunteers. *Eur J Pain* 2012;16:1251–1263.
24. Bachmann CG, Muschinsky S, Nitsche MA et al. Transcranial direct current stimulation of the motor cortex induces distinct changes in thermal and mechanical sensory percepts. *Clin Neurophysiol* 2010;121:2083–2089.
25. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113.
26. Sharpe L, Nicholson Perry K, Rogers P, Dear BF, Nicholas MK, Refshauge K. A comparison of the effect of attention training and relaxation on responses to pain. *Pain* 2010;150:469–476.
27. Hsieh AY, Tripp DA, Ji LJ, Sullivan MJ. Comparisons of catastrophizing, pain attitudes, and cold-pressor pain experience between Chinese and European Canadian young adults. *J Pain* 2010;11:1187–1194.
28. Modir JG, Wallace MS. Human experimental pain models 2: the cold pressor model. *Methods Mol Biol* 2010;617:165–168.
29. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol* 1999;82:1934–1943.
30. Cruccu G, Aziz TZ, Garcia-Larrea L et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007;14:952–970.
31. Lefaucheur JP. Use of repetitive transcranial magnetic stimulation in pain relief. *Expert Rev Neurother* 2008;8:799–808.
32. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurol* 2007;6:188–191.
33. Zheng X, Alsop DC, Schlaug G. Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. *Neuroimage* 2011;58:26–33.
34. Antal A, Brepohl N, Poreisz C, Boros K, Csifcsak G, Paulus W. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clin J Pain* 2008;24:56–63.
35. Csifcsak G, Antal A, Hillers F et al. Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. *Pain Med* 2009;10:122–132.
36. Mylius V, Jung M, Menzler K, Haag A, Khader PH, Oertel WH, Rosenow F, Lefaucheur JP. Effects of transcranial direct current stimulation on pain perception and working memory. *Eur J Pain* 2012;16(7):974–982.
37. Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *Eur J Neurol* 2008;15:1124–1130.
38. Boggio PS, Amancio EJ, Correa CF et al. Transcranial DC stimulation coupled with TENS for the treatment of chronic pain: a preliminary study. *Clin J Pain* 2009;25:691–695.
39. Rosen AC, Ramkumar M, Nguyen T, Hoeft F. Noninvasive transcranial brain stimulation and pain. *Curr Pain Headache Rep* 2009;13:12–17.
40. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. *Neurology* 2008;70:2329–2337.
41. Mitchell LA, MacDonald RA, Brodie EE. Temperature and the cold pressor test. *J Pain* 2004;5:233–237.
42. Vaksvik T, Hetland K, Rokkum M, Holm I. Cold hypersensitivity 6 to 10 years after replantation or revascularisation of fingers: consequences for work and leisure activities. *J Hand Surg Eur Vol* 2009;34:12–17.
43. Campbell DA, Kay SP. What is cold intolerance? *J Hand Surg [Br]* 1998;23:3–5.

