American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 5 (May), 2016: pp 600-605
Available online at www.jpain.org and www.sciencedirect.com

High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial

Andrew Flood,*,† Gordon Waddington,†,‡ and Stuart Cathcart*,†

**Centre for Applied Psychology, and ‡Discipline of Physiotherapy, Faculty of Health, University of Canberra, Canberra, Australian Capital Territory, Australia.*
†University of Canberra Research Institute for Sport and Exercise, University of Canberra, Canberra, Australian Capital Territory, Australia.

Abstract: Transcranial direct current stimulation (tDCS) is a form of brain stimulation that allows for the selective increase or decrease in the cortical excitability of a targeted region. When applied over the motor cortex it has been shown to induce changes in cortical and subcortical brain regions involved in descending pain inhibition or conditioned pain modulation (CPM). The aim of the current study was to assess whether activation of pain inhibitory pathways via tDCS of the motor cortex facilitates the CPM response. Elevated CPM after active tDCS of the motor cortex was hypothesized. Thirty healthy male volunteers attended 2 experimental sessions separated by 7 days. Both sessions consisted of CPM assessment after 20 minutes of either active or sham (placebo) tDCS over the motor cortex. CPM capacity was assessed via the pain-inhibits-pain protocol; CPM responses were shown to be elevated after active compared with sham tDCS. This report concludes that tDCS of the motor cortex enhances the CPM response in healthy men. This finding supports the potential utility of tDCS interventions in clinical pain treatment.

***Perspective:** The use of noninvasive brain stimulation over the motor cortex was shown to enhance the CPM effect. This finding supports the use of tDCS in the treatment of chronic pain, particularly in sufferers exhibiting maladaptive CPM.*

***Key words:** Transcranial direct current stimulation, conditioned pain modulation, brain stimulation.*

Transcranial direct current stimulation (tDCS) is a form of brain stimulation shown to induce focal, prolonged, and yet reversible shifts in cortical excitability.[28] These shifts are polarity dependent, with anodal tDCS resulting in neuronal depolarization and enhanced neuronal excitability, and cathodal stimulation induces neuronal hyperpolarization and decreased neuronal excitability.[28] Therefore, tDCS allows for the selective increase or decrease in the excitation of a targeted cortical region.

Support has been shown for the use of tDCS in a wide range of settings including the treatment of depression[4] and the enhancement of memory[16] and problem-solving ability.[10] Similarly, tDCS of the motor cortex can influence pain perception in healthy subjects[5] and chronic pain sufferers.[1]

In an attempt to uncover the underlying mechanisms of this pain-modulating effect, computer modeling and functional imaging have been used to track the current flow and resulting changes in cortical excitation resulting from tDCS of the motor cortex. This research has shown current flows affecting not only the immediate, targeted cortical regions, but also remote regions such as the cingulate cortex, insula, thalamus, and brainstem.[12] It is argued that these remote effects may be due to the modulation of their functional interaction with the motor cortex through cortico–subcortical connectivity.[23]

The facilitation of pain inhibitory pathways may explain the analgesic effects of tDCS of the motor cortex. Diffuse noxious inhibitory control (DNIC) explains the pain-inhibits-pain phenomenon whereby a noxious stimulus applied to one region of the body acts to inhibit the activity of pain-processing dorsal horn neurons in

Received June 11, 2015; Revised December 18, 2015; Accepted January 11, 2016.
The authors have no conflicts of interest to declare.
Address reprint requests to Mr. Andrew Flood, BSc Psych (Hons), Centre for Applied Psychology, Faculty of Health, University of Canberra, University Drive, Bruce, Canberra, Australian Capital Territory 2610. E-mail: Andrew.Flood@canberra.edu.au
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2016.01.472

extrasegmental regions.[24] This process has been described in animals to involve a complex spino–bulbo–spinal loop devoid of higher brain center involvement.[11] Conditioned pain modulation (CPM) is the preferred terminology when referring to this endogenous pain inhibitory process in humans because it acknowledges the influence of top-down activity from higher order brain structures and also bottom-up pain modulation via the spino–bulbo–spinal loop.[7,25,39]

Research on cortical activity during CPM activation in humans has shown prolonged activity in higher cortical structures similar to those affected by tDCS of the motor cortex, including the cingulate, insula, and thalamus.[3,7,11,25,29] It is possible then that the commonly observed analgesic effects of tDCS of the motor cortex may be due to the facilitation and therefore enhanced activation of CPM pathways.

This hypothesis has been previously supported by the findings of Reidler et al,[33] who discovered that anodal tDCS of the motor cortex significantly enhanced CPM. However, methodological issues significantly limit the ability to draw definitive conclusions from the findings of Reidler and colleagues.[33] For example, CPM is typically assessed using the pain-inhibits-pain protocol, whereby one painful stimulus, the conditioning stimulus (CS), inhibits the perceived intensity of a second painful stimulus, the test stimulus (TS), presented to a spatially remote bodily region.[26] In the study by Reidler and colleagues,[33] these 2 painful stimuli were presented simultaneously. This is in contrast to the alternative approach in which the CS and TS are instead presented sequentially. The protocol adopted by Reidler and colleagues,[33] referred to as the parallel CPM protocol, has been argued to result in an inflated inhibitory response because it may be influenced by attention or distraction effects.[40]

In addition, low-definition tDCS—such as that used by Reidler et al,[33] administers a constant current typically through 2, 35-cm^2 sponge electrodes.[6,8,27] This approach has been shown to induce widespread changes in cortical activation, thereby reducing the clarity of the resulting behavioral effects.[6,8,14] Recent advancements have led to the development of high-definition (HD) tDCS (HD-tDCS), which uses smaller electrodes arranged in a ring configuration. This form of stimulation allows for more focal stimulation, with peaks in current flow localized to the area underlying the targeted region.[22]

Thus, the aim of the current study was to examine the effects of HD-tDCS of the motor cortex on CPM in healthy volunteers. It was hypothesized that anodal HD-tDCS targeted at the motor cortex will result in significant increases in the observed CPM effect.

Methods

Participants

Because of the known age-[19] and sex-[30] related differences in CPM capacity, participation was restricted to pain-free men between the ages of 18 and 40 years. Specific criteria excluded individuals with current pathology to the hands, sufferers of diseases with the potential to cause neural damage such as diabetes, as well as sufferers of chronic pain. Individuals were also excluded on the basis of documented contraindications to tDCS (eg, implanted medical devices or history of epilepsy).[13] Thirty participants (mean age 23.9 years) were recruited through advertisements placed throughout the University of Canberra and local community. On the basis of previous research,[33] this sample size was considered adequate. All participants received both stimulation conditions (sham and active) in a randomized, counterbalanced order. Randomization was achieved using a computer-driven random number generator. This ordering was conducted by the principal researcher (A.F.) at the time of participant arrival.

tDCS

HD-tDCS was delivered via a 4 × 1 HD-tDCS multichannel stimulation interface (Model 4X1-C2, Soterix Medical, New York, NY) attached to a conventional 1 × 1 tDCS device (Model 1300, Soterix Medical). Electrodes were placed in a 4 × 1 ring configuration using plastic casings inserted into an electroencephalography recording cap. The center anode electrode was positioned over the area corresponding to C3; an approximation of the location of the left motor cortex on the basis of the international 10/20 electroencephalography system. Return electrodes were placed in a radius surrounding the anode electrode at locations approximately corresponding to Cz, F3, T7, and P3.

Participants' hair underneath the electrode was parted so as to reduce current impedance. Also, conductive gel (Signa Gel; Parker Laboratories Inc, Fairfield, NJ) was injected into the plastic casing beneath the electrode to improve conductance. The HD-tDCS device was used to assess impedance or conductance values before stimulation. Adjustments were made to ensure that these values did not exceed 1.50 quality units.

In the active HD-tDCS condition, 2 mA was delivered for 10 minutes. The HD-tDCS device automatically implemented the ramping method whereby the current intensity is gradually increased to reach the target intensity (2 mA) within 30 seconds, where it is maintained for the desired duration (10 minutes). At the end of this period, current intensity is then gradually ramped back down to 0 mA. This protocol has been shown to induce localized shifts in cortical excitability beyond the stimulation period of up to 6 hours.[22] Similar protocols have been shown to be well tolerated by participants.[6]

In the sham condition, the same protocol was adopted, however, current intensity was ramped up to 2 mA and immediately back down to 0 mA at the start and end of the 10 minute stimulation period. Similar protocols have been shown to produce an effective control condition whereby participants are blinded to their condition.[6,18]

Measures

Pressure Pain Threshold

Participants were instructed to place their right hand on a table with their palm facing down. Pressure was