Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Transcranial direct current stimulation (tDCS) and the cardiovascular responses to acute pain in humans

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ARTICLE INFO

HIGHLIGHTS

- We tested whether transcranial direct current stimulation (tDCS) alters both pain perception and its cardiovascular responses and if it impacts basal hemodynamics.
- Active tDCS did not affect resting hemodynamics or autonomic outflow.
- Only with the least painful stimulus, tDCS modestly reduced perceived pain and the peak cardiovascular and autonomic responses.

ABSTRACT

Objective: To determine if transcranial direct current stimulation (tDCS) reduces both acute pain perception and the resultant cardiovascular responses.
Methods: Data were acquired on 15 healthy subjects at rest and in response to three cold pressor tests: 0, 7, and 14 °C. Subsequently, single sessions of sham and active anodal tDCS (2.0 mA for 40 min) were delivered to the left primary motor cortex (M1).
Results: Perceived pain was reduced only after active tDCS with the 14 °C cold pressor test. This was accompanied by tendency for lesser increases in heart rate ($\sim$2 beats/min, $p = 0.09$) and blood pressure ($\sim$3 mm Hg, $p = 0.06$). The effect size of tDCS on peak heart rate and blood pressure responses at 14 °C was 0.47 and 0.54, respectively. On the other hand, baseline heart rate, blood pressure, leg blood flow, and leg vascular resistance were unaffected by tDCS. No other responses were affected.
Conclusions: Our results demonstrate that M1 anodal tDCS has no effect on basal hemodynamics or cardiovascular autonomic outflow and has only modest effects on the responses to acute pain in healthy humans.
Significance: Application of tDCS shifts the pain perception threshold in healthy individuals but does not significantly modulate efferent cardiovascular control at rest or in response to pain.
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1. Introduction

In humans, acute painful stimuli increase heart rate, blood pressure and sympathetic nervous activity to the vasculature (Lewis, 1942). If one could modulate the responses to acute pain, this might have broader application to not only reduce the somatosensory burden of pain but also mitigate against its possible long-term cardiovascular effects (Goodson et al., 2013). One approach to treat pain is direct brain stimulation. However, until the 1990s only surgically implanted electrodes to achieve deep brain stimulation had been systematically tested and shown to induce significant decreases in pain. More recently, non-invasive, easy to administer approaches have generated increased interest as a potential therapeutic intervention (Fregni et al., 2007; Jensen et al., 2013). Transcranial direct current stimulation (tDCS) has long lasting modulatory effects on cortical function and allows a reliable sham-stimulation condition to assure specificity of effects. Therefore, tDCS might provide a testable avenue to both reduce pain perception and the resultant cardiovascular responses.

There is evidence that tDCS can effectively modulate pain perception threshold in healthy individuals (Boggio et al., 2008; Csifcsak et al., 2009), indicating that its analgesic effects do not depend on aberrant neural activity. Beyond altering afferent pain

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perception, there is data suggesting that brain stimulation could modulate efferent cardiovascular control (Schestatsky et al., 2013), and hence has been proposed as a potential tool for the management of hypertension, even independent of pain (Cogiamanian et al., 2010; Schestatsky et al., 2013). For example, high-frequency transcranial magnetic stimulation (TMS) reduces blood pressure and heart rate in rats, apparently through sympathoinhibition (Hong et al., 2002). tDCS-mediated reductions in heart rate and blood pressure have also been observed in humans (Binkofski et al., 2011), though this is not consistently found (de Vries et al., 2010; Floel et al., 2008; Raimundo et al., 2012; Vandermeeren et al., 2010). Even though there is also evidence of the contrary (Vandermeeren et al., 2010), some data suggest potential alterations in cardiac autonomic control with tDCS (Brunoni et al., 2013; Montenegro et al., 2011). However, this work relied on heart rate variability which can be a poor surrogate for direct measures of autonomic control (Taylor and Studinger, 2006).

Directly measured muscle sympathetic outflow via microneurography has shown inhibition of pulse-synchronous activity after TMS (Macefield et al., 1998). In addition, microneurography data indicate that TMS alters sympathetic activity to skin (Silber et al., 2000; Niehaus et al., 1998). Hence, cortical stimulation may alter not only pain perception and its resultant cardiovascular responses but also basal homeostatic hemodynamics not related to pain perception. Nevertheless, despite evidence from TMS studies, direct measurements of the effects of tDCS on muscle sympathetic outflow via microneurography are still lacking.

We tested the hypothesis that non-invasive cortical stimulation alters pain perception and the autonomic responses to acute pain. We chose M1 anodal tDCS to modulate cortical excitability since this montage has shown analgesic effects in the setting of experimental pain in healthy subjects (Boggio et al., 2008; Csifcsak et al., 2009) as well as in chronic pain patients (O'Connell et al., 2014), and because the M1 has been involved in the control of bulbar cardiovascular nuclei and vasomotor spinal preganglionic neurons (Ba-M'Hamed et al., 1996; Viltart et al., 2003). In addition to evaluating any potential changes induced by tDCS on baseline cardiovascular measures, we used the nociceptive response to immersion of the hand in cold water (cold pressor test) at three different temperatures as a provocative maneuver. The cold pressor test increases perceived pain, blood pressure, heart rate, vascular resistance, and sympathetic activity (Fagius et al., 1989), and the responses are directly related to decreasing water temperature (Kregel et al., 1992). A strong link between the perceived pain and the pressor responses is suggested by work showing that partial sedation proportionally reduces both perceived pain and cardiovascular responses to the cold pressor test (Noseir et al., 2003). Hence, by measuring hemodynamic variables (heart rate, blood pressure, leg blood flow, leg vascular resistance), as well as both indirect (RR interval, mean pressure variabilities) and direct indices (muscle sympathetic nerve recordings) of autonomic outflow, this design allowed us to examine whether tDCS alters perceived pain and its reflex cardiovascular responses.

2. Methods

2.1. Subjects

Fifteen healthy young individuals aged 21–30 participated in this study (7 female). All subjects had a body mass index between 18.5 and 29.9 kg/m^2 and a normal resting electrocardiogram (ECG). None of them had any signs or symptoms of cardiovascular or neurological diseases, recent weight change, regular use of tobacco, or current pregnancy. All subjects gave written informed consent prior to participating. This study was approved by the Institutional

Review Board at Spaulding Rehabilitation Hospital (Protocol #2011-P-001879/1) and conformed to the Declaration of Helsinki.

2.2. Procedures

Subjects visited the laboratory on two separate mornings (around 8 a.m.) to receive either active or sham tDCS. Study visits were separated by a minimum of 7 days to a maximum of 8 weeks. Subjects abstained from vigorous exercise for 2 days prior to each study visit to avoid autonomic and neuroendocrine effects of exercise. In addition, subjects refrained from caffeine and alcohol for the previous 24 h.

Upon arrival, participants were instrumented for tDCS and physiologic assessments, as detailed below. On each visit, assessments were performed first at baseline while no brain stimulation was being delivered, and then again during either active or sham tDCS. Over the two study visits, participants underwent one session of active and one session of sham tDCS. These two interventions were delivered in random and counterbalanced order.

Throughout the protocol, subjects were supine on a laboratory table and were instrumented for measurement of standard lead II of the ECG, beat-by-beat blood pressure in a finger of the left hand (Portapres, Finapres Medical Systems), brachial oscillometric blood pressure (Dash 2000, GE), respiratory excursions from a respiratory bellows placed around the chest, and popliteal artery blood flow velocity at the popliteal fossa of the left leg (Multi-Dop T2 4-MHz Doppler probe; Compumedics DWL, Singen, Germany). After instrumentation and calibration, multiunit postganglionic muscle sympathetic nerve recording from the common peroneal nerve was successfully obtained in a single session (either sham or active tDCS) in 12 subjects.

For all subjects in both sessions, data were acquired during a 5-min period of quiet rest and in response to three cold pressor tests (0, 7, and 14 °C) performed in random order. For each cold pressor test, a 1-min baseline period was followed by 3-min immersion of the right hand in cold water. During the immersion, subjects rated their perceived pain on a Visual Analog Scale for pain every 30 s (0–10, with 0 corresponding to absence of pain and 10 corresponding to the worst imaginable pain). Cold pressor tests were separated by 10 min, allowing hand temperature to normalize between trials. Subsequently, either sham or active tDCS was applied.

Active and sham tDCS were delivered using 35 cm^2 sponge electrodes. The anode was placed over the left primary motor cortex (M1), corresponding to C3 in the International 10–20 Electroencephalography System, and the cathode over the right supraorbital area. An ActivaDose® II Iontophoresis Delivery Unit (ActivaTek Inc., Salt Lake City, UT) was used in all experiments. In active tDCS, current was ramped up over a period of 30 s until reaching 2.0 mA, which were applied for the remainder of the testing session (40 min). Current density was 0.057 mA/cm^2. For the sham condition, the same instrumentation was used but direct current was only applied for 30 s (Gandiga et al., 2006). tDCS was administered by an unblinded investigator who was not involved in data analysis. Subjects were blinded to the type of stimulation and the tDCS device was kept out of their sight for the duration of the study.

Once 5 min of stimulation (active or sham) had elapsed, data were again acquired during a 5-min period of quiet rest and in response to the three cold pressor tests performed in random order while the stimulation continued to be delivered.

2.3. Data and statistical analysis

Values were derived for mean blood pressure ([2 × diastolic + systolic]/3) and for leg vascular resistance (mean blood pressure/leg blood flow). Resting baseline values pre- and post- sham and active tDCS were derived from 5-min averages