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Research article

Transcutaneous spinal DC stimulation reduces pain sensitivity in humans

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HIGHLIGHTS

- Anodal tsDCS reduces pain sensitivity to painful mechanical pinprick stimuli.
- This is the first evidence that tsDCS sensory effects last longer than 30 min.
- Anodal tsDCS had no effect on pain sensitivity to single electrical pulses.

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ABSTRACT

Non-invasive approaches to pain management are needed to manage patient pain escalation and to providing sufficient pain relief. Here, we evaluate the potential of transcutaneous spinal direct current stimulation (tsDCS) to modulate pain sensitivity to electrical stimuli and mechanical pinpricks in 24 healthy subjects in a sham-controlled, single-blind study. Pain ratings to mechanical pinpricks and electrical stimuli were recorded prior to and at three time points (0, 30, and 60 min) following 15 min of anodal tsDCS (2.5 mA, "active" electrode centered over the T11 spinous process, return electrode on the left posterior shoulder). Pain ratings to the pinpricks of the highest forces tested (128, 256, 512 mN) were reduced at 30 min and 60 min following anodal tsDCS. These findings demonstrate that pain sensitivity in healthy subjects can be suppressed by anodal tsDCS and suggest that tsDCS may provide a non-invasive tool to manage mechanically-induced pain.

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1. Introduction

Neuromodulation by means of direct currents has offered a non-invasive way to alter neural excitability [1–3]. Recently, non-invasive application of direct currents to the spinal cord, termed transcutaneous spinal direct current stimulation (tsDCS), has been employed with promising effects on neurophysiological processing [4,5]. In tsDCS, direct current is applied transcutaneously via one 'active' electrode placed over the spine and a second return electrode over a neutral body part (i.e., where no neuromodulatory effects are expected that could influence the outcome measures).

Effects of tsDCS applied at the lower thoracic vertebral level have been described for the motor [6–8], somatosensory [9], and nociceptive [10,11] systems with encouraging clinical translation in recovering motor function in spinal cord injury patients [12] and reducing pain in restless leg syndrome (RLS [13]). In particular, anodal tsDCS anodal tsDCS amplified the motor component of the H-reflex in healthy subjects by reducing post-activation depression [6] and also shifted the H-reflex stimulus-response curve to

Abbreviations: EPS, electrical pain sensitivity; EDT, electrical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain thresholds; NRS, numerical rating scale; tsDCS, transcutaneous spinal direct current stimulation.

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the left, indicating increased excitability [7]. For nociception and pain, anodal tsDCS suppressed both the nociceptive component of the lower limb flexion reflex [10] and the N1 and N2 component amplitudes of foot-laser evoked potentials (LEPs [11]), as well as reduced pain sensitivity to cold stimuli [11]. Thus, anodal tsDCS has been shown to affect the pain system on a spinal, cortical, and perceptual level. (Please see [5] for tsDCS review.)

Perceptual effects following anodal tsDCS have, however, been limited to cold pain, where anodal tsDCS proved beneficial in healthy subjects [11], and to symptom ratings in RLS patients, where it reduced their subjective rating of their instantaneous symptom severity [13]. In an effort to further investigate the potential of anodal tsDCS to modulate pain in particular, we therefore, tested the effects of 15 min of thoracically-applied anodal tsDCS on subjective pain ratings given to mechanical and electrical stimuli particularly focused on small-diameter, thinly-myelinated A-delta fibers, associated with "first pain". Since LEPs and cold pain, A-delta fiber-dependent measures, were suppressed by anodal tsDCS, we expected that anodal tsDCS would likewise reduce pain ratings to pinpricks and electrical stimuli, corresponding to a suppression of pain sensitivity.

2. Material and methods

2.1. Subjects and study design

The study was conducted on 24 healthy right-handed male subjects aged 20–33 years (mean 25 ± 3) after approval from the local Ethics Committee of Ruhr-University Bochum (No. 4549-12). Each subject provided written informed consent according to the Declaration of Helsinki and was introduced to the procedures before the baseline measurement. Subjects with relevant medical conditions (e.g., diabetes, seizure, migraine, pacemaker, obesity) or use of medication were excluded.

All subjects participated in one session, were assigned to either Group A (anodal tsDCS, $n = 12$) or Group S (sham tsDCS, $n = 12$), and were blind to the stimulation group and polarity. The session consisted of 5 blocks: B (Baseline), tsDCS, T0, T30, and T60 (at 0, 30, and 60 min following tsDCS offset, respectively, (Supplementary Fig. 1). Each test block lasted 15 min and tested electrical detection threshold (EDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS) and electrical pain sensitivity (EPS), in that order. MPS and EPS measurements were interleaved with one another. Details for each test and for tsDCS are provided below. No formal sample size analysis was performed on the basis of this study being an investigative analysis. Rather, we based our recruitment on comparable tsDCS study sample sizes, which are typically below fifteen subjects.

2.2. tsDCS

TsDCS was applied using a constant current battery-driven stimulator (neuroConn GmbH, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes (7 × 5 cm) while the subject was lying comfortably on his right side. Subjects were instructed to rest quietly and limit movement for the stimulation period.

One electrode was centered over the spinous processes of the eleventh thoracic vertebra (T10–T12) and the other on the left dorsal shoulder, as has been described previously [9]. Polarity of stimulation refers to the electrode over the spinal process.

During the tsDCS block of the experimental session, one 15-min period of either anodal or sham tsDCS was applied. For anodal stimulation, +2.5 mA was applied for 15 min [6,7,9], resulting in a current density of 0.071 mA/cm^2 and a total charge of 63.9 mC/cm^2, both of which are below the threshold for tissue damage [14]. Sham stimulation was applied using −1.5 mA for 45 s to mimic the initial tingling sensation while avoiding any stimulation-induced effects. Both groups were told that tsDCS stimulation would last for 15 min. Two trained investigators (CMF, LMH) performed the measurements.

2.3. Mechanical testing

A selection of quantitative sensory testing (QST) measurements from a standardized test battery [15] was used for mechanical testing. To avoid interactions between subsequent test stimuli, mechanical probing of a 1 cm area surrounding the electrode was applied in a circular manner. All subjects closed their eyes during the assessment and rated each stimulus immediately following its presentation to maintain focus on the presented stimuli.

MPS - Mechanical pain sensitivity was assessed using standardized punctuate probes (PinPrick, MRC-Systems, Heidelberg, Germany) with 0.25 mm-diameter tip to stimulate cutaneous nociceptors [15–19]. Forces of 8, 16, 32, 64, 128, 256 and 512 mN were presented once per run in a pseudo-randomized order, as provided by the QST protocol [15]. Each run is pseudo-randomized separately and a total of 10 runs (i.e., a total of 5 runs to the right leg, 5 runs to the left leg, alternating between runs) make up a block. All blocks used the same pseudo-randomization. Each subject received 5 runs per leg, alternating between the right and left leg, and was asked to rate pain associated with each stimulus using the numerical rating scale (NRS; 0–100). A rating of "0" indicated no pain; a rating of "100" indicated the worst pain imaginable.

MPT - Mechanical pain threshold was tested using the seven previously described pinprick stimuli. Forces were presented in ascending and descending order (up-and-down rule) to identify suprathreshold and subthreshold stimulus intensities. The final threshold was determined by the geometric mean of five just suprathreshold and five just subthreshold stimulus intensities [15,19–21].

Reference data from the foot of 180 healthy subjects defined 73 mN to be the average pain threshold to pinpricks in young healthy males [22], i.e., on average, young healthy males rate pinpricks at or above 73 mN as painful, and those pinpricks below 73 mN as non-painful. Since we were specifically interested in anodal tsDCS's effects on explicitly painful stimuli, pinpricks were categorized based on this population data as either suprathreshold (128, 256, 512 mN) or subthreshold (8, 16, 32, 64 mN), here defined as $MPS_{128–512\,mN}$ and $MPS_{8–64\,mN}$, respectively.

2.4. Electrical testing

Bilateral electrical test stimuli were applied 5 cm proximal to the knee using a custom-built multi-pin electrode following a previously-established paradigm (DS7A, Digitimer, UK) [21,23]. To achieve spatial summation within the receptive field of spinal cord neurons, 12 of these electrodes were mounted in a small circular plastic frame (attached to the skin by double-adhesive tape) and were stimulated simultaneously, which delivers a very high local current density at very low stimulus currents. Owing to the high impedance of the skin surface and rapid breakdown of current density in deeper tissue layers, this electrode has a high selectivity for nociceptive primary afferents located in superficial epidermal layers and avoids excitation of mechanoreceptive axons in subepidermal skin layers [24,25]. Accordingly, electrical stimuli delivered through this electrode have a predominantly "pricking" pain character already at threshold and over a high dynamic range of suprathreshold stimuli [23,25,26]. This "prickling" sensation has been attributed to activation of A-delta fibers such that pinpricks are thought to particularly test mechanosensitive A-delta fiber-mediated percept [27]. A strap electrode attached around the

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