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Highlights

Thoracic transspinal Direct Current Stimulation (tsDCS) delay afferent pain signalling.
In parallel, subjective experience of pain decreased.
Effects increased after stimulation; tsDCS might be a treatment of peripheral pain.
Effect of transspinal direct current stimulation on afferent pain signalling in humans

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Abstract

Anodal transspinal Direct Current Stimulation (tsDCS) has been suggested as a means to treat neuropathic pain by reducing pain signalling/processing and Laser Evoked Potentials (LEPs) likewise as a method to evaluate such reduction. However, results in previous studies are disagreeing. To evaluate these claims using rigorous methodology.

LEPs were evoked from hands and feet in healthy volunteers. The N2 potential and three psychophysic parameters (general- and pinprick pain, warmth) were used to evaluate the signalling and appreciation of pain respectively. This was made at three time points; at baseline, directly- and 30 minutes after low thoracic tsDCS (20 minutes, 2.5 mA, cathode on shoulder). The study was randomized, cross over, double blinded and placebo controlled.

At the **group level**, low thoracic anodal tsDCS produced reduced perceptions of all three tested pain qualities from the foot (p < 0.05 – p < 0.001). These reductions began during stimulation and became more pronounced during the 30 minutes after its cessation (p < 0.05 – p < 0.01). The LEP parameter alteration mirroring these changes was latency prolongation (p < 0.05 – p < 0.001) whereas amplitude reductions were in par with **placebo** stimulation. Similar but less pronounced and only transient (during stimulation, p < 0.05 – p < 0.001) changes, were seen for hand stimulation. The **interindividual** variation was large.

The findings indicate that anodal tsDCS may become a technique to treat neuropathic pain by reducing pain signalling/processing and LEPs likewise a method to evaluate such reduction.

Keywords

transspinal; Direct Current Stimulation; pain; neuromodulation
Introduction

Pain constitutes a large part of the clinical spectrum in people searching aid from health care systems. Neuropathic pain often becomes chronic and is difficult to treat pharmacologically [1]. One common such problem is the pain often afflicting people with polyneuropathy in whom pain with various qualities is reported mainly from feet and legs [2].

Neuromodulation, *i.e.* mainly different stimulation techniques, have increasingly been described during later years as a means to counteract various imbalances of the central nervous system [CNS; 3]. Concerning pain experienced from lower extremities, one theoretically appealing concept is to block and/or modulate pain signalling at the spinal level. Indeed, reports have been presented indicating that this may be an option. Mostly, the technique used is transspinal direct current stimulation (tsDCS). In the majority of the reports [e.g. 4-8] favourable results have been seen using anodal stimulation. However, the number of subjects has often been small, and some result have actually been negative [e.g. 9-11].

The aim of the present study was to thoroughly evaluate if the tsDCS technique may hold its promise and become one of the therapy options for neuropathic pain in clinical practice. To fulfil that aim, we studied a fair number of healthy adults using objective (laser evoked potentials; LEP) and subjective (pain ratings) measures of pain, pain stimulation above and below the spinal level of tsDCS stimulation, using a randomised, cross over, double blinded and placebo-controlled design.
Methods

The study was approved by the regional ethical committee (Linköping University) and the Helsinki Declaration. Written informed consent was obtained from all participants.

Subjects

Nineteen healthy subjects, 24±3 years old (mean, standard deviation; ♂/♀; 10/9) were included. None used analgesics or other psychotropic drugs.

Study design

This was a randomized, double-blind, placebo controlled cross over study. All subjects participated in two sessions 6 ± 1 days apart (mean, standard deviation). This time will well allow for any effect to dwindle [6, 25]. At each session, individual pain thresholds to laser stimulation on the dominant side (self-defined; two left handed) were determined on the dorsum of the foot and hand respectively. LEP recordings were made at three-time points on both locations; at baseline, immediately (T0) and 30 min after ended anodal tsDCS (T30).

Stimulation; tsDCS

Two seemingly identical constant current electrical stimulators, code marked by the producer (Sooma Oy, Helsinki, Finland), were used. (The code was broken after the last stimulation.) The verum stimulator delivered a constant electrical current of 2.5 mA for 20 min (as in most previous studies) whereas the placebo stimulator did so for only for 20 seconds where after it returned to zero. The current was delivered through two electrodes (rubber, 7x5 cm, in sponges soaked in physiological saline, total charge of 63,9 mC/cm²). Automatic control of
resistance would have hindered stimulation at a resistance above 15 mΩ. This never happened. The electrodes were fixed to the skin by adhesive tape with the subject in prone position; the anode over the spinous process of the 10th thoracic vertebra (longer axis parallel to the spine) and the cathode on the shoulder on the dominant side. During stimulation, subjects lay still and were questioned every 5 min whether they had a perception from the electrodes.

Evaluation; LEP and psychophysics

LEP stimulation was performed using a neodymium: yttrium–aluminium–perovskite (Nd; YAP) laser (Stimul1340, DEKA Ltd, Calenzano, Italy, wavelength: 1340 nm, pulse duration 10 ms, spot diameter 4 mm). First, electroencephalography (EEG; Fz, Cz, Pz, T3, T4, A1, A2 according to the 10-20 system and both mastoids; M1, M2) and electrooculography (EOG; forehead and lateral to the eyes) surface electrodes (White Silver electrode ACCE120100, Cephalon A/S, Nørresundby, Denmark) were applied. The LEP recording was made using standard technique aiming to define the N1 and N2 potentials [9]. At the start of each session, after achieving a comfortable position, the pain thresholds for the dorsum of the hand and foot were determined: Starting at 1 J, increasing in steps of 0.25 J, three stimuli were given per level. The pain threshold was defined as the intensity where three consecutive stimulations produced a sharp but endurable pricking pain. This intensity was thereafter used at the respective location during that session. The subjects were instructed to focus on the sensation produced by the stimulations. Stimuli were given with 6-15 seconds interstimulus interval at random locations in a ca 5 * 5 cm large area. For each round of stimulation (20/30 stimuli; hand/foot respectively), the subject determined three psychometric parameters using digitized visual analogue scales (VAS); level of general-, pinpricking- and heat pain (scale for all 0-20; 0: none, 20: extreme).
The LEP responses were recorded using a 64-channel amplifier (SynAmps RT, Compumedics Neuroscan, Charlotte, USA) and analysed with neuroimaging software (CURRY 7; Compumedics Neuroscan and MATLAB 2017B; Mathworks Inc, Natick, Massachusetts, USA). The responses were evaluated by two of us (HR, MS). Epochs containing artefacts were identified visually and discarded. An averaged N1-potential (the signal from the temporal electrode contralateral to the side for laser stimulation; T3 or T4, referenced to Fz) and N2 potential (the signal from the Cz electrode referenced to the average of M1 and M2) were calculated. The N1 potential was defined as the first distinct negative peak and the N2 and P2 potentials as the largest negative and positive peak respectively in the post-stimulus interval 0 – 500 ms. The peak latencies and amplitudes (N1; baseline to peak, N2; N2 peak to P2 peak) were then assessed. (Thus, strictly, the amplitude of N2 was that of the N2-P2 complex.)

Statistical analysis

After verifying normal distribution (Shapiro-Wilk), inference testing (paired t-test and linear correlation analysis) were performed. A p-value < 0.05 was considered significant.
Results

During stimulation, with both verum and placebo, all subjects experienced an initial, weak itchy feeling under the spinal electrode and after stimulation, a slight redness was seen on both electrode locations (19/38 stimulations). No other discomfort was reported. When asked after each session, the subjects could not indicate above chance level, whether they had been exposed to verum or placebo.

The N1 potential was not possible to conclusively determine for most stimulations. Therefore, this parameter was not further considered. For the N2 potential, this could be decisively delineated in all but seven and three stimulations (placebo/verum) respectively, distributed over six individuals (1-2 stimuli per individual).

Group values

Values of LEP- and psychophysic parameters are given in Fig. 1-2. Concerning LEP parameters, the general tendency during the experiment was for amplitudes to fall and latencies to increase. For amplitudes, this was true to the same extent for both modes of stimulation at both locations but more pronounced for stimulations of the foot. Regarding psychophysic parameters from hand stimulation, estimation of pricking pain was reduced after placebo stimulation, slightly more so after verum ditto. Appreciations of general pain and warmth, were reduced directly after verum stimulation, remaining at that level 30 minutes later. The same pattern was seen for estimations from placebo stimulation of the foot. Verum stimulation however, produced estimation reductions of all three parameters that became increased during the 30 minutes after the end of stimulation.

For hand stimulation, there were no significant linear correlations between LEP- and psychophysic parameters. For foot stimulation (verum only), positive correlations were found between changes (i.e. reductions) of N2 amplitude and changes of ratings of general- as well
as pricking pain \((r = 0.88, 0.83, p = 0.02, 0.03)\). A negative correlation \((r = -0.79, p = 0.04)\) prevailed between absolute values of N2 latency and rating of general pain at T30.

**Individual values**

There were large interindividual differences concerning all parameters investigated. Results for the two most salient parameters of the study (N2 latency and pain rating from *verum* foot stimulation) are given in Fig. 3.
Discussion

Anodal tsDCS has been suggested as a means to treat neuropathic pain by reducing afferent pain signalling and/or processing and LEP likewise as a method to evaluate such reduction [e.g. 4, 7]. The present study aimed at testing these claims using rigorous methodology. Our findings indicate that both claims have reasonably sound grounds. Thus, at the group level, low thoracic anodal tsDCS produced reduced perceptions of all three tested pain qualities from painful stimulation of the foot. These reductions began during stimulation and became more pronounced during 30 minutes after its cessation. The LEP parameter mirroring these changes was latency (prolonged) whereas amplitude reductions were in par with those produced by placebo tsDCS. Thus, in contrast to many previous tsDCS studies, but in accordance with the experience from other modes of evoked potentials, latency proved to be the most robust parameter. Similar but, compared to painful foot stimulation, less pronounced and only transient (during tsDCS stimulation) effects on LEP parameters and pain perception, were seen for painful hand stimulation.

Concerning LEP analysis, we aimed at describing the N1 as well as the N2 potential but were unable to distinctly detect the former in the majority of subjects. Most previous studies have dealt with the N2 potential and a recent publication demonstrated that tsDCS only affects this, not the N1 potential [7]. In any event, as a tool for clinical evaluation, the N1 potential does not seem to be sufficiently robust. During the experiment, effects of the study set up per se were seen in terms of latency prolongation, and even more pronounced, amplitude reduction of the N2 potential. There may be many reasons for this such as habituation (physiologic and psychologic; [7], reduced attentiveness etc. [12, 13]. At any rate, these confounders produced by the experimental situation, must be minimized using rigorous methodology as in the
present study or results may be compromised. Failure to do so, may be one reason for conflicting results in previous tsDCS studies.

A rather large number of reports concerning effects of tsDCS on spinal function including that of pain processing have been published. Early and recent experimental studies have demonstrated that DC stimulation applied both intraspinally and epidurally affects local neuronal functioning \(\text{e.g.} \ 14, 15\) and that at least some effects of DC stimulation in animals and humans closely resemble each other \(16\). It has also been shown that spinally applied DC stimulation, apart from more local effects \(17\) may have effects without delay and at large distances such as regarding function of the cerebral cortex including aspects that might relate directly to pain perception \(18-20\). These findings may be due to far field effects of the induced electric field and thus depend on the localisation of the return electrode \(21-23\). By all reason, they could also be due to afferent activity induced in spinal tracts. Such mechanisms may thus explain the findings of our study concerning effects on pain processing and perception from body parts, the afferent activity of which enter the spinal cord well above the level of tsDCS stimulation \(i.e.\) the hand, as previously reported for motor function; \(24\).

The field of neuromodulation is by many regarded as promising. One major obstacle in its development is the fact that effects of stimulation vary both intra- but even more interindividually. Such findings have been reported also for the tsDCS technique \(23, 25, 26\). And now in the present study (Fig. 3). This has created doubts regarding the prospects of these techniques. One might argue the opposite; this opens the possibility for individualized medicine. Non-invasive neuromodulation lends itself well to this concept due to its very low risk of producing harm. Nonetheless, there is still a need to study effects of different stimulation parameters such as dosing and placing of electrodes \(22, 23, 27\). Some backgrounds to variability may be controlled for, \text{e.g.} the kind of brain derived neurotrophic
factor (BDNF) present in the individual to be treated, since this affects the effects of tsDCS [28].

Conclusions

Our results demonstrate that tsDCS affects pain signalling and pain perception in healthy subjects. This indicates that the technique may become a therapeutic alternative for pain treatment. The optimal modes of stimulation still need to be defined. Since there is a large interindividual variability in terms of response to stimulation, the latter may have to be individualized. This might be done through placebo-controlled test sessions as has been shown for prediction of effects on motor cortex excitability of tDCS over long time periods [29]. If available, defining the individual’s BDNF genotype may aid the decision process.
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Conflict of interest/Disclosure

Potential conflict of interest: No conflict.
References


Figure legends

Figure 1. Group values of LEP parameters (N2 amplitudes and latencies [broken ordinate]; mean and standard error of the mean, the latter indicated in one direction). Three time points: BL; baseline, T0; directly after cessation of tsDCS stimulation, T30; 30 minutes after that cessation. Hand and foot-, (upper and lower row), placebo and verum stimulation, (blue and red symbols respectively). *; p < 0.05, **; p < 0.01, ***; p < 0.001; asterisks close to a connecting line refer to comparison over the corresponding time (BL-T0, T0-T30), far from the line to the entire study time (BL-T30), colouring as for corresponding lines.

Figure 2. Group values of psychophysic parameters (pain, pricking pain and warmth; mean and standard error of the mean, the latter indicated in one direction). Three time points: BL; baseline, T0; directly after cessation of tsDCS stimulation, T30; 30 minutes after that cessation. Hand and foot-, (upper and lower row), placebo and verum stimulation, (blue and red symbols respectively). *; p < 0.05, **; p < 0.01, ***; p < 0.001; asterisks close to a connecting line refer to comparison over the corresponding time (BL-T0, T0-T30), far from the line to the entire study time (BL-T30), colouring as for corresponding lines.

Figure 3. Individual values (different colours, verum stimulation of foot) of N2 latency (left, broken ordinate) and appreciation of general pain (right) for the 19 subjects at the three timepoints.
Figure 1

![Graphs showing amplitude and latency changes between baseline (BL), T0, and T30](image)

- **Amplitude (µV)**
- **Latency (ms)**

- **BL**: Baseline
- **T0**: Time 0
- **T30**: Time 30

- **Significance Levels**:
  - ***: p < 0.001
  - *: p < 0.05

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- **Amplitude Graphs**:
  - Blue line: BL
  - Red line: T0
  - Green line: T30

- **Latency Graphs**:
  - Blue line: BL
  - Red line: T0
  - Green line: T30
Figure 2

General pain (VAS)

Pricking pain (VAS)

Heat pain (VAS)

BL T0 T30 BL T0 T30 BL T0 T30

5

4

3

2

1

0

1

2

3

4

5

6

7

8

9

10
Figure 3

Latency (ms)

General pain (VAS)

BL  T0  T30

BL  T0  T30