Original Experimental

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Neuromodulation of somatosensory pain thresholds of the neck musculature using a novel transcranial direct current stimulation montage: a randomized double-blind, sham controlled study

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Abstract

Objectives: Anodal transcranial direct current stimulation (tDCS) of primary motor cortex (M1) and cathodal of the primary sensory cortex (S1) have previously shown to modulate the sensory thresholds when administered with the reference electrode located over the contralateral supraorbital area (SO). Combining the two stimulation paradigms into one with simultaneous stimulation of the two brain areas (M1 + S1 – tDCS) may result in a synergistic effect inducing a prominent neuromodulation, noticeable in the pain thresholds. The aim of this study is to assess the efficacy of the novel M1 + S1 – tDCS montage compared to sham-stimulation in modulating the pain thresholds in healthy adults.

Methods: Thirty-nine (20 males) subjects were randomly assigned to either receiving 20 min. active M1 + S1 – tDCS or sham tDCS in a double-blinded single session study. Thermal and mechanical pain thresholds were assessed before and after the intervention.

Results: There were no significant differences in the pain thresholds within either group, or between the M1 + S1 – tDCS group and the Sham-tDCS group ($p>0.05$), indicating that the intervention was ineffective in inducing a neuromodulation of the somatosensory system.

Conclusions: Experimental investigations of novel tDCS electrode montages, that are scientifically based on existing studies or computational modelling, are essential to establish better tDCS protocols. Here simultaneous transcranial direct current stimulation of the primary motor cortex and primary sensory cortex showed no effect on the pain thresholds of the neck musculature in healthy subjects. This tDCS montage may have been ineffective due to how the electrical field reaches the targeted neurons, or may have been limited by the design of a single tDCS administration. The study adds to the existing literature of the studies investigating effects of new tDCS montages with the aim of establishing novel non-invasive brain stimulation interventions for chronic neck pain rehabilitation.

North Denmark Region Committee on Health Research Ethics (VN-20180085)

ClinicalTrials.gov (NCT04658485).

Keywords: acute pain; healthy subjects; neuromodulation; primary motor cortex; primary sensory cortex; QST; quantitative sensory testing; tDCS; transcranial direct current stimulation.

Introduction

Neck pain can be a disabling condition with impact on the quality of life and the functional capacity of the patients [1]. Neck pain has a world prevalence of 4.6–5.3%, which makes it the 4th most common cause of disability out of 291 conditions from the Global Burden of Disease 2010 study [1]. Moreover, neck pain ranks as the 21st most burdensome of these conditions measured in disability adjusted life years [1].

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One way to reduce pain is to increase the somatosensory pain threshold. For this purpose, transcranial direct current stimulation (tDCS) has shown potential [2].

tDCS is a type of non-invasive neuromodulation, that induces acute changes in cortical excitability [3]. In general anodal stimulation has an excitatory effect on the cortex while cathodal stimulation has an inhibitory effect in healthy subjects [4, 5]. In both cases, tDCS stimulates neurons on a subthreshold level [6]. The effects of tDCS has shown to prevail after ended stimulation and can last up to several days after a single stimulation session [6]. The long-term effects of tDCS are likely driven by activity-dependent synaptic plasticity that occurs as a result of the subthreshold modulation of the neuronal membrane potentials at the targeted cortical area [7, 8]. The modulation of the stimulated cortical area is thought to produce changes in the activity of connected brain areas and thereby exert its effects more widespread [7].

As the research field of neuromodulation is expanding there is a standing call for exploratory studies, with rigorous methodology and strong sample sizes, examining various configurations of the available tDCS technologies, to strengthen the predictability of the clinical outcome [9–12]. To date, there is no general consensus on which configuration of tDCS produces the most effective analgesic effect so attempting to identify new promising stimulation parameters is necessary [13]. Currently the most utilized tDCS configurations are anodal tDCS (a-tDCS) of primary motor cortex (M1) with the cathode placed over the contralateral supraorbital area (SO), which has been shown to significantly reduce pain perception [2, 14–17]. Cathodal tDCS (c-tDCS) of the primary somatosensory cortex (S1) with the anode placed over SO has likewise shown to significantly reduce pain perception [17–19]. Recent technological advancements of the tDCS has provided the opportunity to stimulate at multiple targets simultaneously; e.g. the M1 and the dorsolateral prefrontal cortex in the montage named unihemispheric concurrent dual-site stimulation by Vaseghi et al. [20]. Targeting multiple sites which are functionally connected have shown improved modulatory effect in terms of larger and longer lasting changes in cortical excitability [17, 20]. As the S1 and M1 are functionally connected in somatosensory pain processing via cortico-cortical pathways [10, 21–23], it is possible to design a network-focused tDCS montage using only the two electrodes available in conventional tDCS equipment. Despite the M1 and S1 individually being targets of interest for several tDCS studies, no existing studies have investigated the analgesic effects of a combined simultaneous a-tDCS of M1 and c-tDCS of S1 montage (M1 + S1 – tDCS). Therefore, the aim of this study is to investigate the efficacy of the novel M1 + S1 – tDCS on modulating the somatosensory system by administering the montage to a healthy population in a double-blinded sham controlled experiment and assessing the effects on the pain thresholds of the corresponding muscle structures; in this case the descending part of musculus trapezius.

Methods

Participants

Forty healthy participants (20 male) in the age 18–30 years were included in this study conducted at the Department of Health Science and Technology, at Aalborg University, between 01/09/2019 and 01/11/2019. All participants provided written, informed consent and filled out a questionnaire prior to beginning the experiment. The sample size was determined based on detecting a medium to large effect size (Cohen's d≥0.5), with 80% power and an alpha level of 0.05. The effect size was based on existing literature with positive findings [2]. Exclusion criteria included acute or chronic pain, pregnancy, drug addiction, use of alcohol, opioids, antipsychotics and benzodiazepines as well as any diagnosed diseases that affects the somatosensory nervous system. The study was performed according to the Helsinki Declaration, approved by the North Denmark Region Committee on Health Research Ethics (VN-20180085), and was registered at ClinicalTrials.gov (NCT04658485).

Study design

A randomised double-blinded sham controlled study design. The included participants were stratified by gender (males, females), and randomized into two equal groups: active tDCS (n=20) and sham tDCS (n=20). The general timeline of a participant is illustrated in Figure 1.

Transcranial direct current stimulation

The tDCS were administered using a two-channel tDCS system (Sooma Medical, Finland) with 25 cm^2 sponges (Sooma ComfoPads) moistened with a 0.9% NaCl (saline) solution.

The active tDCS group received 20 min. of continuous stimulation at an intensity of 2 mA. The stimulation intensity and duration is in line with previous studies showing somatosensory modulation using tDCS [2, 15, 16–19, 24–27]. Electrode impedances were continuously monitored and the device automatically shut off, if the impedance exceeded 15 kΩ.

The sham tDCS group received 30 s stimulation ramping up to the 2 mA intensity, and then shutting off at the beginning and the end of the 20 min. session. These parameters were preconfigured by a third party in the stimulation device software, so the experimenter was supposed to be blinded to the condition, for the double-blind design. As a result of this design the blinding of the experimenter was assumed, but was not tested. The sham tDCS configuration mimics the sensory experience of active tDCS, and has been validated in previous studies [28–30]. However, due to recently raised issues with the sham

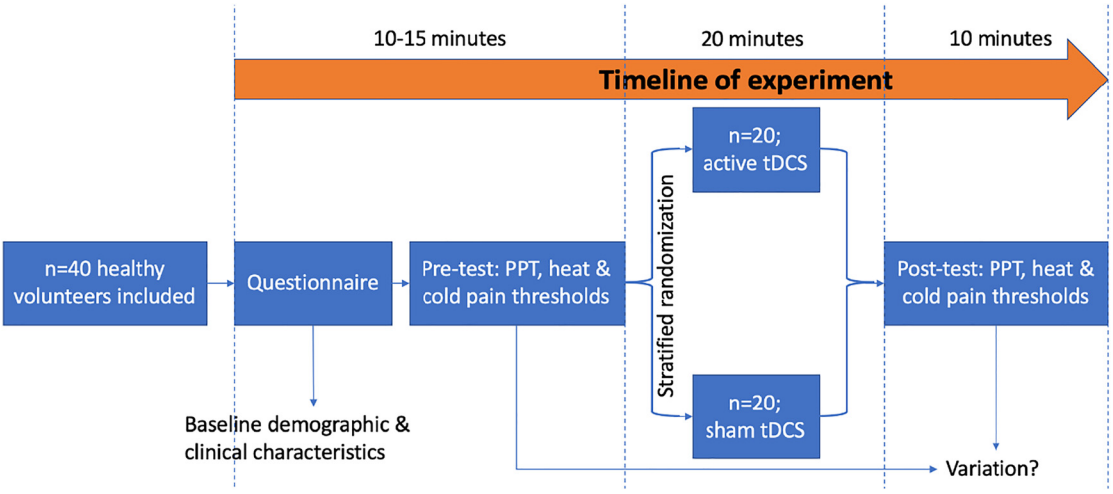

Figure 1: Illustrates the general timeline of the study.

condition in specific study designs it is preferred that subjects are naïve to the sensory experience of active tDCS [31, 32]. This is ensured by running a parallel-group study design instead of a cross-over design so the subjects are not able to compare the sensory experiences between the two stimulation configurations.

The electrical field distribution shown in Figure 2 is modelled in the software NIC2 (Neuroelectrics, Spain). The anode electrode was placed over C4 according to the EEG 10–20 system on the basis of the cortical homunculus as well as a previous study which had found this to be the approximate location of the area representing the neck region in M1 [33]. The cathode electrode was placed at P3, over S1 according to the EEG 10–20. This tDCS montage is referred to as M1 + S1 – tDCS.

Pressure pain thresholds (PPT)

The PPT was measured on the right side of the descending part of m. trapezius; dexter medial trapezius and on the m. flexor carpi radialis on the right forearm as a control (PPTC). The assessment followed the standardized Quantitative Sensory Testing (QST) protocol of the German Research Network on Neuropathic Pain (DFNS) [34]. For this a manual pressure algometer (SOMEDIC, Sweden) with a pressure area of 1 cm^2 and application rate on 30 kPA/s was used. The mean threshold value across three trials were categorized as (PPT) for the dexter medial trapezius and as (PPTC) for the control site on the right forearm for further analysis.

Thermal pain thresholds (TPT)

The TPT were measured using a 3 × 3 cm (9 cm^2) contact thermode on the skin above the right side of the descending part of m. trapezius using the PATHWAY pain & sensory evaluation system (Medoc Advanced Medical Systems, Israel). TPT were measured using the methods of limits. Each stimulus series began with ascended and descended in ramps starting from a baseline temperature of 32 °C and gradually increasing and decreasing temperature at a rate of 1 °C/s. Cold pain thresholds (CPT) and heat pain thresholds (HPT) were

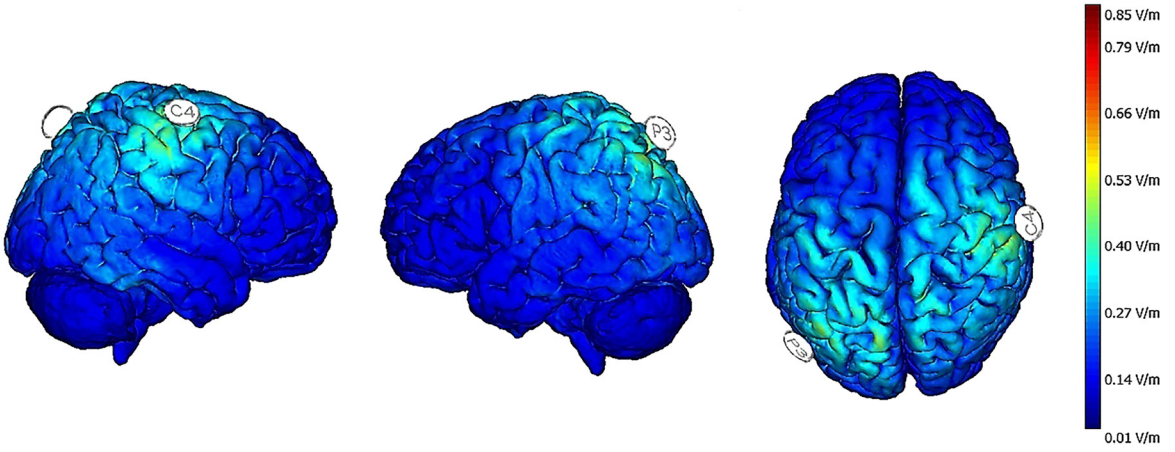

Figure 2: Illustrates the electrical field distribution of the active stimulation (Anode placed over C4 and cathode over P3). The model is made using the modelling program in Neuroelectrics stimulation software.

assessed by the participants with the button press as soon as the thermal sensation first became painful. The measurements were repeated three times, within the temperature range of 0–55 °C and the average was used for analysis in accordance with the QST protocol described by the DFNS [34].

Statistics

Data are presented as mean ± standard deviation (SD) in text, tables and figures. The statistical software (IBM SPSS 26) was used to perform all frequentist statistical analysis. Significance was accepted at $p \leq 0.05$. The psychophysical data were evaluated for normal distribution using the Shapiro-Wilk's test of normality. In case of a non-normal distribution a log-transformation was conducted and used for further analysis. To analyze for baseline differences between the two groups a one-way analysis of variance (ANOVA) with groups (Sham tDCS and Active tDCS) as between group factor was performed using the pre-intervention data (Table 1).

A two-way mixed-model ANOVA was performed for each of the sensory threshold modalities (PPT, PPTC, CPT and HPT) with groups (Sham tDCS and Active tDCS) as between group factor and time (pre-intervention and post-intervention) as within-group factor.

If significant main effects or interactions were found, post hoc analysis was done using a Bonferroni test to correct for multiple comparison. As the two-way mixed model ANOVA assumes sphericity, a Greenhouse-Geisser correction was utilized when required.

Table 1: Baseline demographics.

	Active tDCS	Sham tDCS	Total
N participants	20	19	39
Male	10	10	20
Female	10	9	19
Age	22.10	21.70	21.90
Weight	71.75	70.37	71.08
Height	174.00	175.50	174.73

Results

One participant was excluded after ended session, as she reported to have misunderstood the assessments resulting in a total of 39 (20 male) participants (mean age 21.9 ± 2.3 years) included for the analysis.

The mean values of the pain thresholds are presented in Table 2, followed by the differences between pre and post-intervention in Table 3.

Baseline thresholds between groups

The groups were not significantly different at baseline in either the thermal or pressure pain thresholds as determined by one-way ANOVA: HPT: $F(1, 37)=0.10$, $p=0.76$, CPT: $F(1, 37)=0.22$, $p=0.64$, PPT: $F(1, 37)=0.37$, $p=0.55$, PPTC: $F(1, 37)=0.14$, $p=0.71$.

This is illustrated in Figures 2 and 3.

Differences before and after intervention and between groups

The results of the Two-Way Mixed ANOVA showed that there was no significant difference on the main effect time: PPT: $F(1, 37)=0.73$, $p=0.40$, $\eta^2=0.02$; HPT: $F(1, 37)=1.05$, $p=0.31$, $\eta^2=0.03$; CPT: $F(1, 37)=0.03$, $p=0.86$, $\eta^2=0.00$; PPTC: $F(1, 37)=0.51$, $p=0.48$, $\eta^2=0.01$.

Similarly, there were no interaction between the factors time and group in any of the modalities: PPTR: $F(1, 37)=0.22$, $p=0.64$, $\eta^2=0.01$; HPT: $F(1, 37)=0.93$, $p=0.34$, $\eta^2=0.03$; CPT: $F(1, 37)=0.02$, $p=0.89$, $\eta^2=0.00$; PPTC: $F(1, 37)=0.01$, $p=0.94$, $\eta^2=0.00$.

Table 2: Mean values of the pain thresholds.

	HPT [mean °C ± SD]		CPT [mean °C ± SD]		PPT [mean kPa ± SD]		PPTC [mean kPa ± SD]	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Sham tDCS	45.67 ± 3.88	45.64 ± 3.62	9.5 ± 8.24	9.7 ± 9.23	386.79 ± 174.72	403.14 ± 165.28	412.88 ± 217.99	421.95 ± 227.73
Active tDCS	46.03 ± 3.48	45.5 ± 3.17	8 ± 5.15	9.99 ± 8.13	355.25 ± 146.57	363.67 ± 153.98	374.88 ± 131.31	386.38 ± 153.63

Table 3: Mean difference of the thresholds between pre and post-intervention.

	HPT [difference °C ± SD]	CPT [difference °C ± SD]	PPT [difference kPa ± SD]	PPTC [difference kPa ± SD]
Sham tDCS	−0.04 ± 1.22	0.2 ± 5.43	16.35 ± 83.57	9.07 ± 69.84
Active tDCS	−0.53 ± 1.87	1.99 ± 6.64	8.42 ± 77.06	11.5 ± 75.59

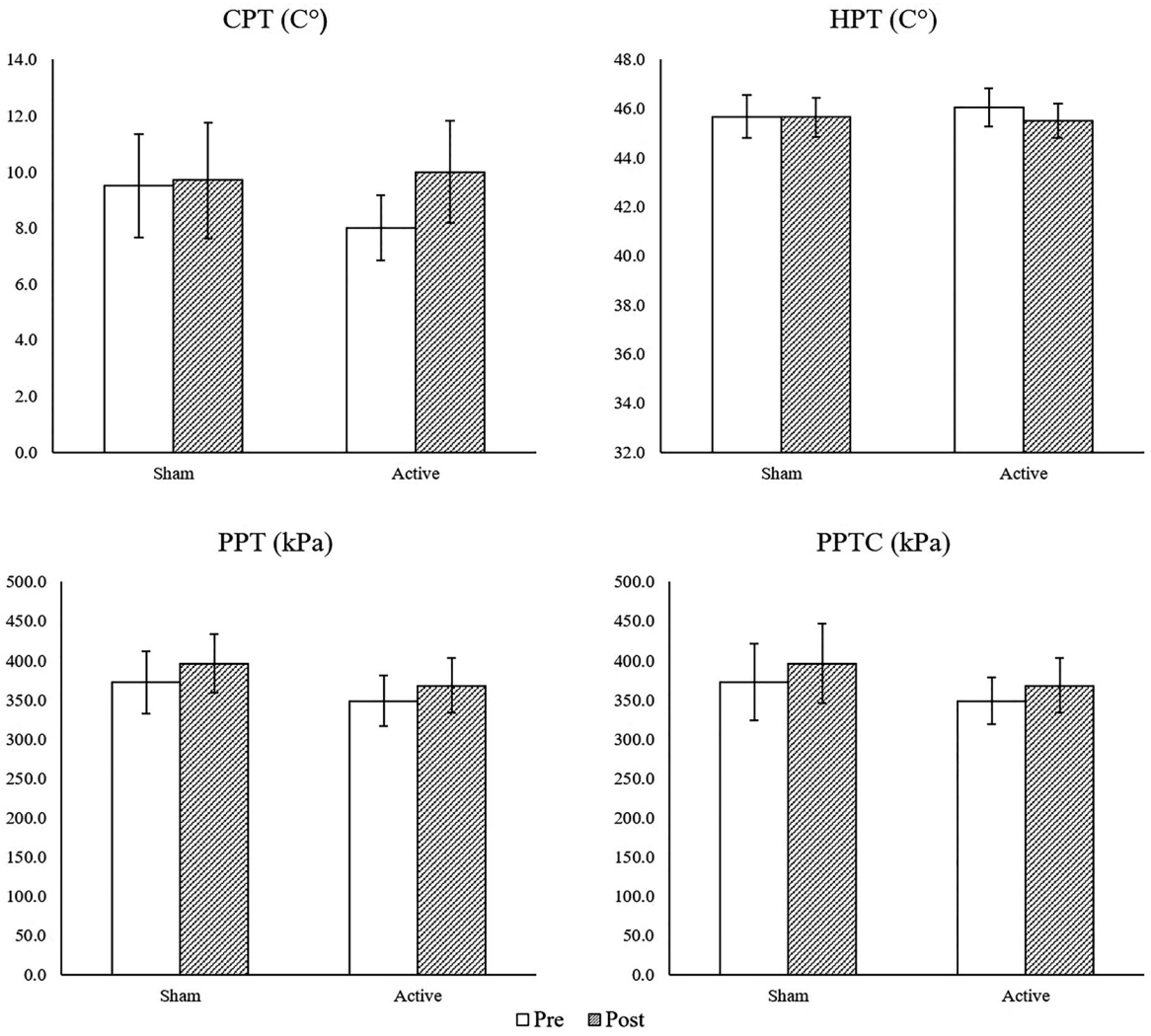

Figure 3: Mean (±SEM) cold pain threshold (CPT), heat pain threshold (HPT), pressure pain threshold (PPT) and pressure pain threshold of the control area (PPTC) before (non-shaded) and after (shaded) tDCS. CPT and HPT represents the temperature at which the participants identified the temperature as painful. PPT and PPTC represents the threshold at which the participants identified the pressure as painful.

Overall the present data could not show a significant modulation of the pain thresholds by the active tDCS when compared with the sham tDCS.

Discussion

Summary of findings

This is the first study investigating the effects of the tDCS montage with simultaneous anodal M1 a-tDCS and S1 c-tDCS (M1 + S1 tDCS). The results of this study showed no significant difference in heat pain thresholds, cold pain thresholds, and pressure pain thresholds between the active tDCS group and the sham tDCS group. Likewise, no significant difference was observed between the thresholds before and after intervention within the two groups.

Comparison with existing studies using conventional a-M1 tDCS or c-S1 tDCS

As the present study investigated a novel tDCS configuration no studies exist with exact comparable methods. However, it is relevant to compare the modulatory results of this configuration with the more investigated M1 a-tDCS and S1 c-tDCS configurations, that both have the reference electrode located over the contralateral supraorbital area (SO). These studies with similar methodology show varying results. Studies that report results in line with the present

study include Jürgens et al. [26] and Aslaksen et al. [24]. These studies both investigated the effect of a-tDCS on M1, and showed no significant analgesic effect on heat pain threshold [24, 26]. Jürgens et al. [26] performed tDCS and sham stimulation on 17 healthy participants in a blinded crossover design with 15 min of 1 mA a-tDCS. Similarly Aslaksen et al. [24] reported no significant differences between active and sham stimulation following 7 min of 2 mA a-tDCS. Vaseghi et al. [17] investigated the effect of 20 min of 0.3 mA c-tDCS on S1 on pressure pain thresholds in a double-blinded randomized sham controlled study, which showed no significant differences between the active and sham conditions.

Conversely, a number of other studies have reported positive findings. A meta-analysis by Vaseghi et al. [2] on the effects of a-tDCS of M1 showed a significant increase in pain threshold with an effect size of 22.19%. Notably, the five studies included in the meta-analysis used diverse methodology, different sample sizes ranging from 8 to 20, and applied different stimulation protocols in terms of current intensity, duration and electrode sizes [2].

Similarly a meta-analysis on c-tDCS of S1 showed a significant increase in pain threshold in healthy subjects with an effect size of 11.62% [35]. However, the majority of these studies, administering c-tDCS of S1 did not have a control condition, and all had a smaller sample size compared to the present study [35].

When examining the existing literature it is evident that there is a large variation in stimulation protocols. Consequently, a direct comparison of the present findings with previous studies might be misleading. Therefore, it is relevant to discuss how intervention design may have affected the results of this study.

Intervention design

By placing the electrodes over the right side M1 and left side S1, it was possible to achieve simultaneous a-tDCS of M1 and c-tDCS of S1. Utilizing this tDCS montage, it was investigated whether simultaneous stimulation of both brain areas involved in somatosensation and pain processing would induce a modulatory effect on the pain thresholds. The non-significant results of this study, however, indicate that the M1-S1 tDCS montage is ineffective. One possible explanation for this is that the current may not have run transcranially but along the scalp, and as a result, the neurons in the deeper layers of the cerebral cortex were not effectively polarised. This is not possible with the conventional M1-tDCS montage, as the receiving electrode is placed in manner that leads the current directly through the head.

Another explanation could be, that the close proximity of the electrodes shapes the pathway of the current, in a way that it is perpendicular to the cortical neurons, which does not result in polarization [36].

The present study consisted of one single session of tDCS. Repeated stimulations might have been more suitable, since the aim of this study was to induce a modulation of pain thresholds, which could be used to treat chronic neck pain. Guidelines on the therapeutic use of tDCS advice against the use of single-session studies as these may not produce clinically significant results [37]. Additionally, the most common tDCS protocol used for treating pain conditions includes five consecutive days of stimulation. This is supported by empirical studies, which report that repeated stimulations are necessary to induce a long-term effect with tDCS [38–40]. Consequently, a possible explanation for the non-significant results might be that a single-session tDCS did not cause the glutamate-mediated neuroplasticity necessary to induce the long-term effects of tDCS [6]. In order to further examine the potential of this M1-S1 tDCS configuration, future research could investigate the effect of a multiple-session design on modulating pain thresholds.

Another important difference to consider of the present tDCS configuration compared to existing studies is the electrode size. The comparable studies used electrodes with 35 cm^2 diameter, compared to 25 cm^2 diameter electrodes used in the present study [2, 24, 41]. This size change results in a difference in the stimulation intensity delivered at the cortical level, which is assumed to correlate with level of induced modulation [42].

Finally by utilizing the M1-S1-montage the SO, which is the conventional cathode location [11], will not receive stimulation, which it does in the conventional M1-tDCS montage. The involvement of the SO in somatosensation and pain processing is not fully elucidated. A study by Nitsche and Paulus [3] suggests that M1 stimulation is only effective in modulating, when the cathode is located over the contralateral SO. However, this study did not include a montage which involved S1, and has not since been revalidated. Thus, it is relevant to investigate whether the reference electrode can be utilized in an alternative way to produce a greater modulatory effect of tDCS.

Limitations

Some methodological limitations have to be considered to contextualize the findings. The effect of the M1 + S1 tDCS on the somatosensory system is presently quantified using assessments of thermal and pressure pain thresholds.

These methods have been utilized and validated extensively [34, 43]. However, it is possible that the analgesic effect of tDCS is not reflected at pain threshold level. In clinical research on chronic pain patients the outcome of the tDCS is usually reported in terms of a pain score [44, 45]. This is not possible in the current design as the assessment is aborted as the pain is first experienced. A supra-pain threshold or pain tolerance assessment would have been interesting to include in the design, as it may have provided a different perspective. However, looking at the existing tDCS literature in healthy subjects it appears that focusing on pain thresholds is the standard method [21].

Another possible limitation of the present study is that the efficacy of the blinding was not assessed. The present study is designed to be double blinded, however neither the subjects or the experimenters were tested to see if they could identify the stimulation type that were administered. The blinding of the subject receiving the stimulation has previously been validated [32], but the double blinding aspect of the present study was designed internally and should be tested for reliability. This weakens the reliability of the blinding.

Conclusions

Designing and testing novel stimulation protocols is necessary for developing more efficient and reliable tDCS-based treatments for chronic pain conditions. In this study, a novel tDCS montage with anode over M1 and cathode over S1 to modulate the pain thresholds of healthy young adults was investigated. The results showed no significant effect on thermal and pressure pain thresholds within the sham group as well as within the active tDCS group. Furthermore, there were no significant modulatory differences between the active tDCS group and the sham group. Despite the null-findings of the present study, this study may inspire future research in optimization of tDCS-parameters to strive for better treatment options.

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Competing interests: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The study was performed according to the Helsinki Declaration, approved by the North Denmark Region Committee on Health Research Ethics (VN-20180085), and was registered at ClinicalTrials.gov (NCT04658485).

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