Article

Efficacy of direct current stimulation on experimental sensory modalities and pain outcome measures in healthy participants: systematic review and meta-analysis.

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Abstract: Background: Objectives. The objective of this study was to compare the efficacy of direct current stimulation (DCS) applied at the transcranial, suboccipital and spinal level on experimental sensory modalities and pain outcome measures in healthy subjects. The hypothesis of this study was that systematic analysis of the efficacy of DCS on modulating evoked thermal and mechanical pain modalities and mechanisms such as endogenous pain modulation in healthy individuals would reveal sensitive outcome measures help develop this technique for the control of chronic pain.

Materials and Methods. Database searches were conducted up to December 2019 for randomized controlled trials that performed sham-controlled DCS of experimental sensory modalities and pain outcomes following transcranial, suboccipital and spinal locations in healthy participants. Standardized mean differences with 95% confidence intervals were calculated for sensory modalities, including random-effect metanalysis.

Results: Thirty-one studies were included for analysis (647 participants). A significant decrease in pain intensity for active vs sham transcranial stimulation was identified for pain intensity ($n=158$; $SMD=0.79$; 95% $CI=0.56$ to 1.02), a significant increase in heat pain threshold ($n=222$; $SMD=1.16$; 95% $CI=0.95$ to 1.37), and a significant increase in cold pain threshold ($n = 155$; $SMD = 0.77$, 95% $CI 0.53$ to 1.01). No significant modulation of pressure pain threshold was identified with DCS and only a limited number of studies focused on experimental pain modulation following neuromodulation at the suboccipital or spinal level.

Conclusions: These results show significant transcranial DCS neuromodulation of pain intensity and on thermal pain modalities. Future studies should focus on endogenous pain and sensory modality modulation with sham-controlled DCS applied at transcranial, suboccipital and spinal locations.

Keywords: Non-invasive direct current stimulation; Cortical, Suboccipital and Spinal stimulation; Quantitative sensory testing, Pain outcome measures, Endogenous pain modulation.

1. Introduction.

Over the last few decades, direct current stimulation has been applied over the scalp as a non-invasive neuromodulation technique to modulate the brain excitability^{1, 2}. Indeed, direct current stimulation (DCS) provide a powerful tool for altering brain activity in a way that can outlast stimulation, and to influence neuronal function². DCS techniques are used in several conditions to relieve pain such as fibromyalgia³, spinal cord injury⁴, migraine⁵, and chronic low back pain⁶. In studies published to date, DCS has been applied over transcranial level, with the aim of modulating excitability at cortical areas such as the primary motor cortex⁷ or the dorsolateral prefrontal cortex⁸, and subcortical areas such as the cerebellum⁹, and spinal cord¹⁰. It has been observed that could exist different mechanisms of action that depends on application modality, current parameters, and location of the DCS^{11, 12}.

Although transcranial direct current stimulation (tDCS) reduces pain intensity in people with different chronic pain^{13, 14}, the effect of this technique to reduce experimental pain in healthy volunteers is controversial^{15, 16}. Furthermore, previous systematic reviews did not compare and evaluate the efficacy of pain modulation following DCS at subcortical sites such as the cortex, suboccipital and spinal level in healthy participants^{13, 17}. A systematic review and metanalysis of the DCS technique would clarify the efficacy of this technique to modulate experimental pain intensity¹⁸, pressure pain thresholds¹⁹, thermal pain thresholds²⁰, endogenous pain modulatory mechanisms such as conditioned pain modulation²¹ and temporal summation magnitude²². The hypothesis of this study is that systematic analysis of the efficacy of DCS on modulating evoked thermal and mechanical pain modalities and mechanisms such as endogenous pain modulation in healthy individuals would reveal sensitive outcome measures to inform future research and clinical application of this stimulation technique.

The objective of this study is to compare the efficacy of direct current stimulation applied at the transcranial, suboccipital and spinal level on experimental sensory modalities and pain outcome measures in healthy subjects.

2. Methods.

A systematic review of the literature was performed following PRISMA guidelines²³. A comprehensive review of computerized literature databases and searches to find unpublished trials were performed to minimize publication bias.

2.1 Strategy of search and study selection.

MEDLINE, accessed by PubMed (1990 to December 2019), EMBASE (1990 to December 2019), CINAHL (1990 to December 2019), Web of Science (1990 to December 2019), PsycInfo (1990 to December 2019), PEDro, and Google Scholar electronic databases were searched using the medical subject headings (MeSH): "transcranial direct current stimulation", "direct current stimulation", "pain", "healthy volunteers", "pain measurement", "cerebellum", "endogenous pain modulation", "nociception", "humans", "transcutaneous spinal direct current stimulation", "pain modulation", "quantitative sensory testing" as well as following free terms, combined in multiple search strategies with Boolean operators in order to find relevant articles: "spinal stimulation", "direct current stimulation", "sensory testing", "participants", "pain measurement", "clinical trials", "humans", "antinociception", "clinical study".

2.2 Eligibility criteria.

We followed the PICOS framework to organize the inclusion criteria. Population (P): study that included healthy subjects without pain in the last 3 months; Intervention (I): studies that use

transcranial-DCS, spinal-DCS or cerebellar-DCS; Comparisons (C): interventional DCS or non-interventional DCS control; Outcomes (O): primary outcome that included quantitative sensory testing; and Study design (S): randomized controlled trials (RCTs) published in Spanish and English language.

Two authors screened the titles and abstracts of the initially identified studies to determine if they satisfied the selection criteria. Any disagreement was resolved through consensus. Full-text articles were retrieved for the selected titles, and reference lists of the retrieved articles were inspected to identify additional publications. The search was limited to studies written in English and Spanish. The search strategy described above yielded 84 results. Only articles reporting data on studies using the above-mentioned neurostimulation techniques in healthy subjects were considered eligible for inclusion. The inclusion criteria were: clinical trials, studies in humans, studies written in English and Spanish, studies that use transcranial-DCS, spinal-DCS or cerebellar-DCS as the intervention, studies in healthy volunteers, assessed variables like conditioned pain modulation, temporal summation magnitude and quantitative sensory threshold. The exclusion criteria were: studies that included participants with previous pain, studies that they did not include the current parameters, and studies that did not use quantitative sensory tests as variable of pain measurement. Thus, 31 studies were selected for analysis in this review, of these, 24 studies used transcranial-DCS, 6 studies used spinal-DCS and 2 studies used cerebellar-DCS (Figure 1).

2.3 Data extraction.

Physiotherapy Evidence Database (PEDro) scoring system was used for evaluating the selected studies²⁴. Two authors independently screened the full-text articles to obtain a score in the PEDro scale. The PEDro tool consists of 11 questions with a maximum score of 10. The following criteria were used for rating the methodological quality of a study: 9 to 10, "excellent"; 6 to 8, "good"; 4 to 5, "fair"; and < 4 "poor"²⁴. All studies were included in the analysis regardless of study quality.

Two independent reviewers (GGB and JFC) analysed the quality of all selected articles using the same methodology. Disagreements between reviewers were resolved by consensus by including a third reviewer. Inter-evaluator reliability was determined using the "kappa coefficient" (> 0.7 means high level of agreement among evaluators, 0.5-0.7 a moderate level of agreement, and < 0.5 a low level of agreement)²⁵. In each study, we extracted the following data to elaborate the characteristics of the table: (1) number of sessions and average age (2) current parameters (intensity, duration, current density, technique and electrode location), and (3) measurements (PT, CPM, and/or TS), (4) results.

2.4 Risk of bias assessment.

In the event of any discrepancies between the 2 reviewers, a consensus was attempted to be reached by discussion. If a full consensus could not be reached between the 2 reviewers after an exhaustive discussion, the opinion of a third reviewer was obtained, and the proceeding majority consensus was taken.

For the qualitative analysis of selected studies, the criteria for classification of evidence was followed for randomized controlled trials^{26,27}. The evidence was classified into 5 levels based on methodological quality as follows: 1) "Strong", consistent findings among multiple high quality randomized controlled trials; 2) "Moderate", consistent findings among multiple low quality randomized controlled trials and/or controlled clinical trials, and/or one high quality randomized controlled trial; 3) "Limited", one low quality randomized controlled trial and/or controlled clinical trial; 4) "Conflicting", inconsistent findings among multiple trials (randomized controlled trials and/or controlled clinical trials); or 5) "No evidence from trials", no randomized controlled trials and/or controlled clinical trials²⁶.

2.5 Data synthesis.

Following the criteria proposed in the IMMPACT consensus statement²⁸ and previous meta-analysis²⁹, we back transformed the standardized mean difference (SMD) to a mean difference using the mean standard deviation of the post-treatment sham group scores of the studies included in this analysis.

Data on each study's design, participant characteristics, intervention(s), outcome(s) and adverse event(s) were extracted from each of the selected studies. Pooled analyses were conducted for the primary outcome of pain intensity post-treatment and at follow-up. Treatment effect was reported as the SMD with 95% confidence interval (CI) using the software of Meta-Analysis (Review Manager "Revman", version 5.4). The statistical significance of grouped SMDs was calculated as Hedges *g*, to consider the possible overestimation of the true effect magnitudes of sample in small studies. The magnitude of the "*g*" was interpreted according to the following scale³⁰: < 0.20 = insignificant effect, 0.20 – 0.49 = small effect, 0.50 – 0.79 = moderate effect, ≥ 0.80 = great effect. Heterogeneity between studies was measured by the "*I*² statistic". An *I*² value exceeding 50% was used as the threshold to identify significant statistical heterogeneity^{31, 32}.

The same inclusion criteria were used for the systematic review, but for inclusion in the meta-analysis, three more criteria were added: 1) the results of studies must have detailed information regarding the comparative statistical data (mean, standard deviation, and 95% confidence interval), 2) the data of analysed variables must be represented in at least two studies included; and 3) a minimum score of 6 points on the PEDro scale for clinical trial studies should be reached to allow their inclusion in the meta-analysis, because the inclusion of low methodological quality studies in a meta-analysis may overestimate the results obtained³³.

3. Results.

Thirty-one studies met the inclusion criteria (Figure 1). Of the 31 studies included in this systematic review, 10 were scored as "excellent" and 21 were scored as "good" on the PEDro methodological quality scale (Table 1).

3.1 Qualitative analysis.

The mean age of subjects included in the review was 26.4 ± 3.7 years. The sample sizes of the included studies were small, between 10 and 41 subjects, except one study that included 75 subjects³⁴. Most of the included studies applied a single stimulation session, with the exception of two studies^{8, 35} that performed 2 sessions; one study with 3 sessions³⁶, 4 sessions³⁷ and 5 sessions³⁸. Table 2 shows the data of included studies.

Regarding the qualitative analysis of included studies a "strong" level of evidence was found for reduction of pain intensity with tDCS^{34, 39-42}, a "limited" level of evidence in suboccipital (cerebellar) DCS⁴³, and a "conflicting" level in spinal-DCS studies^{44, 45}. For heat and cold pain thresholds, a "strong" level of evidence was found for increase of thermal thresholds in tDCS studies^{10, 34, 38, 46-52}. For pressure pain thresholds, a "conflicting" level of evidence was found for the increase of mechanical pain thresholds in tDCS studies^{35, 38, 46, 53, 54}. A "limited" level of evidence was found for temporal summation magnitude in a spinal-DCS study⁴⁵. For conditioned pain modulation a "moderate" level of evidence was found in tDCS studies^{35, 42}, and a "limited" level of evidence in spinal-DCS studies³⁶. Table 3 shows the qualitative data of included studies.

3.2 Quantitative analysis.

For the quantitative analysis of pain intensity modulation with DCS, five studies were included^{34, 40-42, 53}, with the meta-analysis of these studies showing statistically significant differences for the decrease of pain intensity for active compared to control tDCS (n = 158; SMD = 0.79, 95% CI 0.56 to 1.02; Figure 2). Heterogeneity findings were found among the groups ($\text{Chi}^2 = 10.62$; df = 4; $I^2 = 62\%$; $P = 0.03$).

Five studies of pressure pain threshold modulation were included in the review^{35, 38, 46, 53, 54}, with the meta-analysis failing to show statistically significant differences for the increase of mechanical thresholds for active vs control tDCS (n = 82; SMD = 0.06, 95 % CI -0.25 to 0.36; Figure 3). Homogeneity findings were found in the groups ($\text{Chi}^2 = 0.44$; df = 4; $I^2 = 0\%$; $P = 0.98$).

Eight studies of heat pain modulation with DCS were included for analysis^{34, 38, 46-49, 51, 53} showing statistically significant differences for active vs control tDCS (n = 222; SMD = 1.16, 95% CI 0.95 to 1.37; Figure 4). Heterogeneity findings were found in the groups ($\text{Chi}^2 = 71.47$; df = 7; $I^2 = 90\%$; $P < 0.01$).

Eight studies of cold pain modulation with DCS were included for analysis^{8, 10, 38, 46-48, 50, 52}, with the meta-analysis of the studies showing statistically significant differences for active vs control tDCS (n = 155; SMD = 0.77, 95% CI 0.53 to 1.01; Figure 5). Heterogeneity findings were found in the groups ($\text{Chi}^2 = 31.74$; df = 7; $I^2 = 78\%$; $P < 0.01$).

3.3 Adverse and side effects.

Of 31 studies included in this systematic review, 15 registered adverse or side effects were related to DCS interventions^{8, 9, 15, 20, 35, 38, 39, 41-43, 45, 47, 49, 52, 54}. Furthermore, 5 studies registered tingling and itching sensations during the interventions with DCS^{8, 39, 45, 52, 54}.

4. Discussion.

This systematic review and meta-analysis revealed significant DCS neuromodulation of pain intensity and on thermal pain modalities following transcranial cortical application. The effect size for modulation of pain intensity and thermal pain thresholds was large. However only a limited number of studies were found for DCS neuromodulation of experimental pain was found following application at the suboccipital or spinal level. No significant modulation of pressure pain threshold was found with DCS technic and only a limited number of studies focused on experimental pain modulation following neuromodulation at the suboccipital or spinal level.

4.1 The effects of DCS on experimental pain intensity, temporal summation and conditioned pain modulation.

The meta-analysis of selected studies showed that active tDCS was effective in reducing pain intensity (Figure 2). Of 31 studies included, only 5 were selected for analysis, with four studies showing a significant reduction in pain intensity following active tDCS compared to sham tDCS ^{34, 40-42}, and one study finding no significant difference between active and sham tDCS ⁵³. A previous systematic review found similar results regarding pain intensity in healthy volunteers ³⁷. Furthermore, our results support the findings of other meta-analyses studies that found a reduction in pain intensity using tDCS in chronic pain conditions like fibromyalgia ⁵⁵, spinal cord injury ⁵⁶, and chronic orofacial pain ⁵⁷.

Qualitative analysis of the selected studies found a “strong” level of evidence for the reduction of pain intensity in transcranial-DCS studies ^{34, 39-42}, a “limited” level of evidence in cerebellar-DCS studies ⁴³, and a “conflicting” level of evidence in spinal-DCS studies ^{44, 45}. These results were similar to previous DCS systematic reviews regarding the level of evidence for pain intensity modulation with tDCS in people with chronic pain conditions ^{13, 58}. A “moderate” level of evidence was found for a reduction in temporal summation in transcranial-DCS studies ^{47, 53, 59}, and a “moderate” level of evidence for conditioned pain modulation ^{35, 42}. However, a meta-analysis of the effect of tDCS on temporal summation and conditioned pain modulation was not possible as only a limited number of studies were found. Previous systematic reviews have found that modulation of both these pain outcome measures in healthy populations ^{13, 17}, although the application of DCS was combined with other interventions like therapeutic exercise or analgesic medications.

4.2 The effect of DCS on pressure pain thresholds.

The meta-analysis of selected studies did not demonstrate that active tDCS was efficacious for increasing the PPTs (Figure 3). Of the 31 studies selected, only 5 were selected for quantitative analysis, with four studies failing to demonstrate a significant increase of PPT following active tDCS compared to sham tDCS ^{38, 46, 53, 54}, and with only one study showing a significant increase following tDCS group ³⁵. These results do not support the findings of a previous systematic review about the effects of tDCS in chronic pain patients ⁶⁰. Furthermore, in the present systematic review a “conflicting” level of evidence was found for mechanical pain threshold modulation in tDCS studies ^{35, 38, 46, 53, 54}.

4.3 The effects of DCS on heat and cold pain thresholds.

The meta-analysis of selected studies demonstrate that active tDCS was efficacious in increasing cold and heat pain thresholds (Figure 4 y 5). Of the 31 studies included, 12 were selected for quantitative analysis of heat and cold pain thresholds following active tDCS, with six studies showing a significant increase in heat pain threshold in active tDCS groups in front of sham tDCS groups ^{34, 38, 46, 47, 49, 51}, and two studies failing to demonstrate a significant difference between active and sham tDCS ^{48, 53}. For cold pain threshold, seven studies found a significant increase in threshold following active tDCS compared to sham tDCS ^{8, 10, 38, 46, 47, 50, 52}, and only one study failed to show a

significant difference between active and sham tDCS⁴⁸. The majority of published studies support DCS modulation of thermal detection or pain thresholds^{34, 46, 47, 50} or tolerance in healthy participants^{8, 51, 52}. The results obtained in this study are supported by a recent systematic review that found an improvement in thermal pain thresholds¹⁷.

Although the mechanisms are not known by which tDCS selectively modulate thermal pain measures compared to mechanical pain, several pain processing centres have been shown to modulate thermal sensation including the hypothalamic nuclei, preoptic area, amygdala^{61, 62} and thalamus⁶³, some of which have been shown to constitute part of the endogenous pain modulation network⁶⁴.

4.4 Limitations and future directions.

According to the Cochrane Handbook for Systematic Reviews, “potential advantages of meta-analysis include an increase in power, an improvement in precision, the ability to answer questions not posted by individual studies, and the opportunity to settle controversies arising from conflicting claims”. That is, establishing clear methods and specific criteria can minimise the bias that the reviewer brings to the study. However, we cannot limit the bias that is within the literature about DCS¹⁶. The present systematic review was limited to English and Spanish language studies, and most of included studies used small samples that influence in effect sizes and therefore might affect pooled results in the meta-analyses. The major limitation of this systematic review is the lack of DCS studies applied at the subcortical level and spinal level, which would influence the effect size. These studies were not included in the meta-analyses. Another important limitation in the current review is the heterogeneity found in the DCS protocols, with several factors related to current intensity, size of the DCS electrodes, duration of the interventions and the number of sessions^{13, 58}. Furthermore, most of included studies did not perform blinding to clinicians and participants, and only five included studies carried out more than one session with DCS.

Moving one step beyond the state of the art, the next step for DCS is in the clinical field. A translational research application of the main findings supported in the literature could be the inspiring trigger for new research and the identification of the barriers that are contributing factors for solving the gap between the academic field and the clinical practice.

5. Conclusions.

These results show significant transcranial DCS neuromodulation of pain intensity and on thermal pain modalities. Future clinical studies with patients should focus on endogenous pain and sensory modality modulation with sham-controlled DCS applied at transcranial, suboccipital and spinal locations.

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