Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study

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Pain threshold

Abstract

Objective: The primary aim of this systematic review was to evaluate the effects of anodal transcranial direct current stimulation (a-tDCS) on sensory (STh) and pain thresholds (PTh) in healthy individuals and pain levels (PL) in patients with chronic pain.

Methods: Electronic databases were searched for a-tDCS studies. Methodological quality was examined using the PEDro and Downs and Black (D&B) assessment tools.

Results: a-tDCS of the primary motor cortex (M1) increases both STh ($P < 0.005$, with the effect size of $22.19\%$) and PTh ($P < 0.001$, effect size of $19.28\%$). In addition, STh was increased by a-tDCS of the primary sensory cortex (S1) ($P < 0.05$ with an effect size of $4.34$). Likewise, PL decreased significantly in the patient group following application of a-tDCS to both the M1 and dorsolateral prefrontal cortex (DLPFC). The average decrease in visual analogue score was $14.9\%$ and $19.3\%$ after applying a-tDCS on the M1 and DLPFC. Moreover, meta-analysis showed that in all subgroups (except a-tDCS of S1) active a-tDCS and sham stimulation produced significant differences.

Conclusions: This review provides evidence for the effectiveness of a-tDCS in increasing STh/PTh in healthy group and decreasing PL in patients. However, due to small sample sizes in the included studies, our results should be interpreted cautiously. Given the level of blinding did not considered in inclusion criteria, the result of current study should be interpreted with caution.

Significance: Site of stimulation should have a differential effect over pain relief.

1. Introduction

Sensory and emotional processing of pain involves parallel brain structures (Rainville, 2002; Porro, 2003). Lateral thalamic nuclei and the somatosensory cortex (S1) are thought to subserve sensory-discriminative aspects of pain such as threshold, quality, location, and judgement of its intensity, whereas medial thalamic nuclei, the prefrontal cortex and the limbic system are considered to subserve the affective-emotional dimension of pain. The overlap between these areas and emotion-processing regions of the brain could explain the human subjective qualities of pain (Bornhovd et al., 2002; Porro, 2003; Wager et al., 2004).

Brain mapping studies have reasonably consistently identified the brain areas that are active when someone is in pain (Laurent et al., 2000; Peyron et al., 2000). These areas are mostly multimodal and respond to salient non-noxious stimuli as well as noxious stimuli (Mouraux et al., 2011). Brain areas that are...
involved in pain processing signals and are also superficial to the skull are the primary sensory cortex (S1), primary motor cortex (M1), and dorsolateral prefrontal cortex (DLPFC) (Antal et al., 2010).

S1, with its topographical organization, was long presumed to be a key location of pain-related brain activity. However, the evidence behind this notion is not compelling. Some studies clearly show S1 activity is related to pain intensity (Antal et al., 2008; Grundmann et al., 2011) and others show no such relation (Kanda et al., 2000; Peyron et al., 2000; Bingel et al., 2003; Porro, 2003). Some researchers have predicted that S1 activity will most closely relate to pain when the pain is felt in the skin (Simoes and Hari, 1999; Timmermann et al., 2001).

M1 activation can affect pain reduction not only because of neural connections existed between S1 and M1, but also because of functional relationship between M1 and thalamus (Coghill et al., 1999), and activation of thalamus leads to activation of other pain-related structures such as anterior cingulate, and periaqueductal grey areas which have major role in pain management (Tsubokawa et al., 1993; Fomberstein et al., 2013). A vast literature shows that the motor output of M1 changes with pain (Moseley and Brugger, 2009). This includes reduced amplitude and velocity of movement (Lund et al., 1991), altered muscle coordination (Hodges and Moseley, 2003), decreased motor unit discharge rate (Farina et al., 2004; Hodges et al., 2008) and decreased maximal voluntary contraction force (Graven-Nielsen et al., 2002). The mechanisms behind the involvement of M1 are largely unknown but we know that M1 activity has a clear link with the pain network, which makes it an intuitively sensible target of interventions to reduce pain (Apkarian et al., 2004; Baliki et al., 2012).

DLPFC is one of the areas of the brain most commonly activated during pain, regardless of where the pain is felt (Apkarian et al., 2005). Changes in connectivity between the DLPFC and deeper pain-related areas (Baliki et al., 2012) and reduction in grey matter density and DLPFC volume (Apkarian et al., 2004) have been implicated in chronic pain for an alternative result (Scarpazza et al., 2013) and for a compelling argument for disregarding brain volume studies altogether. DLPFC activation does seem to be related to cognitive and attentional processing of noxious stimuli (Peyron et al., 1999; Bornhovd et al., 2002) and probably has a role in modulating pain expectation (Sawamoto et al., 2000) and pain-induced anxiety (Ploghaus et al., 1999).

Non-invasive brain stimulation strategies aimed at modifying corticospinal excitability for different purposes have emerged in recent years. In recent pain studies, transcranial magnetic stimulation (TMS) (Leon-Sarmiento et al., 2013), repetitive transcranial magnetic stimulation (rTMS) (Lefaucheux et al., 2006; Hosomi et al., 2013; Jette et al., 2013; Perocheau et al., 2013) and transcranial direct current stimulation (tDCS) (Flor et al., 1997; Riberto et al., 2011) have been used to modulate pain. tDCS is a common method of modulating the cortical activity of superficial pain-relevant areas; it has been used to treat a variety of clinical conditions, and is a painless technique with minimal side effects (Jeffery et al., 2007; Bolognini et al., 2009). tDCS delivers low direct currents via scalp electrodes to the cerebral cortex that result in the modulation of cortical excitability. A part of this current is shunted through the scalp and the rest flows into the cerebral cortex (Miranda et al., 2006; Nitsche et al., 2008). tDCS is usually applied through two surface electrodes, one serving as an anode and the other as a cathode. Anodal tDCS (a-tDCS, involving the application of an anode over the target area) typically has an excitatory effect on the underlying cerebral cortex by depolarizing neurons, while cathodal tDCS (c-tDCS, involving the application of a cathode over the target area) decreases cortical excitability by inducing hyperpolarization (Nitsche and Paulus, 2000). The proposed mechanism behind immediate effects of tDCS is polarity-dependent shifts of the resting membrane potential and consequent alteration of corticospinal excitability at the stimulation site. The idea is that this alteration leads to facilitation or inhibition of the superficial structures and of deeper and more remote brain areas related to pain modulation (Willis and Westlund, 1997; Petrovic et al., 2000; Casey et al., 2001; Lorenz et al., 2003; Lang et al., 2005). Furthermore, long-lasting effects of tDCS depend on N-methyl-D-aspartate (NMDA) receptor-efficacy changes (Liebetanz et al., 2002). Involvement of NMDA receptors induces neuroplasticity in which transformation of synaptic strength takes place by Long-term potentiation and depression (LTP & LTD) mechanisms (Islam et al., 1995; Nitsche and Paulus, 2001; Liebetanz et al., 2002).

S1, M1 and DLPFC are relatively superficial brain areas that contribute to the neural substrate of pain. Pain can be operationalized into key variables, for example sensory threshold (STh), pain threshold (PTh), and pain level (PL) (Fernandez and Turk, 1992; Bornhovd et al., 2002; Giesecke et al., 2005) although these variables are not closely correlated (Wolff, 1964). Some tDCS studies have reported that excitatory effects of a-tDCS may increase the function of superficial areas of pain neuromatrix led to pain management by increasing the level of STh/PTh (Antal et al., 2008; Csicsas et al., 2009) and decreasing the level of PL (Fregni et al., 2006a, b; Roizenblatt et al., 2007; Antal et al., 2010).

There is now a large literature concerning tDCS for pain relief. Recently, systematic reviews of all tDCS pain-related studies have concluded that insufficient evidence exists to make firm conclusions (O’Connell et al., 2011; Luedtke et al., 2012), a problem compounded by the recent questioning of the assumption that the most commonly used intensity of tDCS can be easily blinded (O’Connell et al., 2012; Russo et al., 2013). These studies raise a very important question: what is the evidence for the effectiveness of a-tDCS in modulating pain according to the site of stimulation? According to the common understanding that S1, M1 and DLPFC make independent contributions to pain, the site of stimulation should have a differential effect over pain relief.

As a result, based on the existed studies, we investigated the site-specific effects of a-tDCS on STh/PTh in healthy individuals and PL in patients with chronic pain. We hypothesized that:

1. STh is modulated immediately after application of a-tDCS over S1 and M1 in healthy individuals.
2. PTh is modulated immediately after application of a-tDCS over S1 and M1 in healthy individuals.
3. PL is modulated immediately after application of a-tDCS over S1 and M1 in patients with chronic pain.
4. Application of sham stimulation to different areas of the brain has no effect on STh/PTh in healthy individuals, nor on PL in patients with chronic pain.

2. Methods

2.1. Inclusion criteria

We included studies that recruited participants over the age of 18 years who were healthy or had experienced chronic pain for more than three months (Smith et al., 2001; Latremoliere and Wolff, 2009). All types of study designs, parallel or cross-over, were included regardless of blinding. Studies that utilised a-tDCS on the S1, M1, or DLPFC in healthy subjects or patients experiencing chronic pain were included if:

1. The subjects were over 18 years of age.
2. The outcome measure was VAS in the patient group or STh/PTh in the healthy group.
3. Sham tDCS or active control was applied (Table 1).
Given the fact that M1, S1, and DLPFC are the only superficial areas of pain neuromatrix which are accessible to stimulate by tDCS, we included studies investigated the effects of a-tDCS on these areas in both healthy (Table 2), and patient group with chronic pain regardless of their pathology (Table 3). All modalities that evoked a sensory or painful sensation were included (i.e., laser, heat, cold, and mechanical stimuli). Moreover, in patient group, chronic pain is specified as a refractory pain which is resistant to medical intervention or drug management more than three month (Smith et al., 2001; Latremoliere and Woolf, 2009). We included studies that placed electrodes over M1, DLPFC, or S1 regions.

2.2. Exclusion criteria

Studies were excluded if:

1. They did not involve brain stimulation.
2. The duration of symptoms for patient groups was unclear.
3. The study used surgical brain stimulators, rTMS, TMS, or electrical stimulation with pulse currents (Table 1).

4. The studies used c-tDCS or other forms of non-invasive brain stimulations (TMS, rTMS, or cranial electrical stimulation); indirect forms of stimulation (caloric vestibular stimulation or occipital nerve stimulation) or invasive forms of brain stimulation involving the use of electrodes implanted within the brain.

2.3. Outcome measures

The outcome measures for STh and PTh were percentage changes in stimulus intensities at which participants reported the onset of sensation (STh) or pain (PTh). For PL in patient groups, we pooled studies that used a visual analogue scale (VAS).

Because the included trials involved post-intervention assessments at varying periods, these were partitioned into short-term and long-term outcomes. ‘Short-term’ was arbitrarily defined as less than one hour after intervention. If a trial had multiple assessments during that period, the assessment performed closest to the intervention was used. ‘Long-term’ was defined as greater than one

### Table 1

<table>
<thead>
<tr>
<th>Inclusion Exclusion</th>
<th>Inclusion Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>18 or more years of age</td>
</tr>
<tr>
<td></td>
<td>Either healthy or suffering from chronic pain (musculoskeletal, neural, or central pain syndrome), anatomical location</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>a-tDCS and sham stimulation</td>
</tr>
<tr>
<td></td>
<td>“no treatment”/sham treatment</td>
</tr>
<tr>
<td></td>
<td>Before and after a-tDCS</td>
</tr>
<tr>
<td>Comparison</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>NAS measured by QST&lt;sup&gt;1&lt;/sup&gt; and LEP&lt;sup&gt;2&lt;/sup&gt; amplitude in healthy individuals and VAS in patients with chronic pain</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized control trial, controlled clinical trials, and pre-post trials</td>
</tr>
<tr>
<td>Data reported</td>
<td>Data that enable analysis and estimation of the effects of a-tDCS and sham stimulation on STh, PTh, and PL</td>
</tr>
<tr>
<td>Type of publications</td>
<td>Peer-reviewed journal articles, regardless of the year of publication English language</td>
</tr>
</tbody>
</table>

1 Quantitative sensory testing.
2 Laser evoked potential.
3 Pain threshold.
4 Pain level.
5 Repeated transcranial magnetic stimulation.
6 Functional magnetic resonance imaging.
7 Positron emission tomography.

### Table 2

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Trial design</th>
<th>No. participants</th>
<th>Stimulation method</th>
<th>Outcome measure</th>
<th>Intervention</th>
<th>Stimulated area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boggio et al. (2009)</td>
<td>Double blinded – Sham controlled</td>
<td>20</td>
<td>E.S</td>
<td>VAS</td>
<td>a-tDCS</td>
<td>V1&lt;sup&gt;1&lt;/sup&gt;, M1&lt;sup&gt;2&lt;/sup&gt;, DLPFC&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hansen et al. (2011)</td>
<td>Pre-post test</td>
<td>19</td>
<td>E.S&lt;sup&gt;1&lt;/sup&gt;</td>
<td>VAS, PREP&lt;sup&gt;2&lt;/sup&gt;, BR&lt;sup&gt;3&lt;/sup&gt;</td>
<td>a-tDCS, c-tDCS</td>
<td>M1</td>
</tr>
<tr>
<td>Bachmann et al. (2010)</td>
<td>Single blinded – Crossover</td>
<td>8</td>
<td>QST</td>
<td>VAS</td>
<td>a-tDCS, c-tDCS</td>
<td>M1</td>
</tr>
<tr>
<td>Grundmann et al. (2011)</td>
<td>Pre-post test</td>
<td>12</td>
<td>QST</td>
<td>VAS</td>
<td>a-tDCS, c-tDCS</td>
<td>S1&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reidler et al. (2012)</td>
<td>Double blinded – Sham controlled</td>
<td>15</td>
<td>QST</td>
<td>VAS</td>
<td>a-tDCS, c-tDCS</td>
<td>M1</td>
</tr>
<tr>
<td>Jurgens et al. (2012)</td>
<td>Pre-post test</td>
<td>17</td>
<td>QST</td>
<td>VAS</td>
<td>a-tDCS, c-tDCS</td>
<td>M1</td>
</tr>
<tr>
<td>Antal et al. (2008)</td>
<td>Pre-post test</td>
<td>10</td>
<td>LASER</td>
<td>VAS, LEP&lt;sup&gt;4&lt;/sup&gt;</td>
<td>a-tDCS, c-tDCS</td>
<td>S1</td>
</tr>
<tr>
<td>Csifcsak et al. (2009)</td>
<td>Pre-post test</td>
<td>10</td>
<td>LASER</td>
<td>VAS, LEP</td>
<td>a-tDCS, c-tDCS</td>
<td>S1</td>
</tr>
<tr>
<td>Ragert et al. (2008)</td>
<td>Double blinded – Sham controlled</td>
<td>10</td>
<td>Tactile discrimination</td>
<td>VAS</td>
<td>a-tDCS, c-tDCS</td>
<td>S1</td>
</tr>
<tr>
<td>Rogalewski et al. (2004)</td>
<td>Single blinded – Sham controlled</td>
<td>13</td>
<td>Tactile perception</td>
<td>VAS</td>
<td>a-tDCS, c-tDCS</td>
<td>S1</td>
</tr>
</tbody>
</table>

1 Visual cortex.
2 Primary motor cortex.
3 Dorsolateral prefrontal cortex.
4 Electrical stimulation.
5 Pain related evoked potential.
6 Blink reflex.
7 Somatosensory cortex.
8 Laser evoked potential.
hour after intervention; long-term outcomes were not included in meta-analyses.

2.4. Methods for identifying studies

We searched for relevant studies published in English. To locate eligible articles, a literature search was performed using PubMed, Physiotherapy Evidence Databases (PEDro), CINAHL, CENTRAL (Cochrane Central Register of Controlled Trials), Scopus, PROquest, SPORtDiscuss, AMI (Australian Medical Index), Ovid Medline, EBM Review, Cochrane, Meditex and PsyCINFO, from their inception to July 2012. All reference lists of retrieved papers were searched to identify additional relevant articles unidentified by initial search strategy. The key search terms were: ‘transcranial direct current stimulation’, ‘tDCS’, ‘sensory perception’, ‘pain’, ‘pain perception’, ‘pain tolerance’, ‘sensory threshold’, ‘pain threshold’, ‘sensory stimulation’ and ‘pain trigger’.

2.5. Selection of the included studies

Two reviewers (B.V. and S.J.) independently screened the titles and abstracts of papers identified in the initial search strategy against the inclusion criteria. If the information in the title and abstract was insufficient to make a decision, the reviewers assessed the full paper to include or exclude the study. All included studies were then double-checked by a full-text appraisal. If the reviewers disagreed, resolution was attempted by discussion. If resolution was not achieved, the third reviewer (M.Z.) was consulted.

2.6. Risk of bias and quality assessment

To assess the methodological quality of included studies, we assessed risk of bias using the Cochrane ‘Risk of bias’ assessment tool outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.2 (Higgins and Green, 2011). Fig. 1 is a methodological quality graph for all included studies. Further quality assessment was conducted for each included study by using the Physiotherapy Evidence Database (PEDro scale) (Moseley et al., 2002; Maher et al., 2003). The PEDro scale includes 10 criteria for internal validity; studies are awarded a point for each criterion met. The PEDro cut-points are 9–10, excellent; 6–8, good; 4–5, fair and below 4, poor (de Morton, 2009). Because some of the studies we identified were not randomised controlled trials, the process was repeated using the Down and Black tool (D&B) (Downs and Black, 1998). The D&B contains 27 questions, of which 25 are graded 0 or 1 (‘yes’, ‘no’ or ‘not determined’), one is scored 0–2 and one, on power, is scored 0–5 (Eng et al., 2007) modified scoring for the final item on power to 0 or 1 (Eng et al., 2007) (Table 4).

2.7. Outcome measures

Our primary outcome measures were the STh and PTh of healthy individuals and PL in patients who suffered from chronic pain. STh is usually measured by quantitative sensory testing (QST) using mechanical, vibration or thermal methods (Chong and Cros, 2004). A subject’s STh is classically defined as the level of stimulus intensity necessary for sensation to be just detectable. PTh is defined as the level of stimulus intensity at which pain is detected. PL in patients with chronic pain showed the average pain that they experience during a day, usually measured by VAS (Bolton and Wilkinson, 1998).

2.8. Subgroup analysis and intervention of heterogeneity

We assessed heterogeneity using the Chi² test and I² statistic. Also, the effect of a-tDCS and sham stimulation on STh, PTh, and PL were measured in the M1 and S1 in healthy participants and in the M1 and DLPFC in patients with chronic pain.

2.9. Data extraction

The following data relevant to the aims of this study were extracted: study design; characteristics of subjects (Table 2) outcome

Table 3

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Trial design</th>
<th>No. participants</th>
<th>Patients</th>
<th>Stimulation area</th>
<th>Intervention</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antal et al. (2011)</td>
<td>Double blinded – Sham control</td>
<td>26</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS, SF-36</td>
</tr>
<tr>
<td>Fregni et al. (2006a,b)</td>
<td>Double blinded – Sham control</td>
<td>17</td>
<td>Spinal cord injury</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS, PGA^6</td>
</tr>
<tr>
<td>D’Agostino et al. (2009)</td>
<td>Double blinded – Sham control</td>
<td>7</td>
<td>Chronic pelvic pain</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS</td>
</tr>
<tr>
<td>Soler et al. (2010)</td>
<td>Double blinded – Sham control</td>
<td>39</td>
<td>Chronic spinal injury</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS</td>
</tr>
<tr>
<td>Boggio et al. (2009)</td>
<td>Double blinded – Sham control</td>
<td>8</td>
<td>Chronic neurogenic pain</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS</td>
</tr>
<tr>
<td>Antal et al. (2011)</td>
<td>Double blinded – Sham control</td>
<td>26</td>
<td>Chronic migraine</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS</td>
</tr>
<tr>
<td>Dasilva et al. (2012)</td>
<td>Double blinded – Sham control</td>
<td>13</td>
<td>Refractory orofacial pain</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS</td>
</tr>
<tr>
<td>Antal et al. (2011)</td>
<td>Double blinded – Sham control</td>
<td>1</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>a-tDCS</td>
<td>VAS</td>
</tr>
</tbody>
</table>

1 Primary motor cortex.
2 Dorsolateral prefrontal cortex.
3 Fibromyalgia impact questionnaire.
4 Supra-orbital area.
5 Motor evoked potential.
6 Patient general assessment.
7 Visual motor cortex.
measures (Table 2) and a-tDCS parameters in both healthy and patient groups (Table 5); and percentages of VAS changes immediately post-intervention compared to baseline (pre-test) and sham values (Tables 6 and 7) (Chong and Cros, 2004). When the SD was not reported, it was estimated using the formula SD = SE /sqrt(n) (n = number of subjects in each group) (Higgins and Green, 2011). When there was uncertainty regarding the information and results and when data were not accessible from figures and graphs, we contacted the corresponding author(s) and requested the mean ± SD of desired outcome measures. Where mean ± SD values were not provided for baseline/control and post-intervention parameters as numerical data, they were pooled out from the graphs with Plot Digitizer software (Joseph, 2011).

A Java-based Plot Digitizer program (Higgins and Green, 2011) was used to digitize scanned plots of functional data. Data were entered into the effect size calculator using REVMAN 5.1 software (Cochrane Collaboration, 2008) (Bax et al., 2007). REVMAN calculates statistical significance of the difference between means, 95% confidence intervals (CIs) for the mean difference and uses Hedges’ adjusted g, which is very similar to Cohen’s d but includes an adjustment for small-sample bias (Deeks and Higgins, 2010). Extracted data were entered into the meta-analysis using the generic inverse-variance method as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

We pooled results using RevMan 5 software (version 5.1). We used a random effects model to conduct separate meta-analyses for different forms of stimulation (a-tDCS and sham). Where more than one data point was available for short-term outcomes, we used the first post-stimulation measure. Two forest plots were generated for each outcome measure. In the first one, the percentage changes in STh, PTh and PL after applying a-tDCS compared to baseline values were assessed. In the second one, the percentage changes in STh, PTh and PL after a-tDCS were compared to the percentage changes after effects of sham stimulation.

3. Results
3.1. Identification and selection of studies

The search strategy identified 283 studies, including 221 duplicates. Screening by title and abstract identified 49 studies as potentially eligible for the review. 31 studies which did not meet inclusion criteria were excluded. Seven studies were identified from hand-searching of the reference lists of included studies, of which one were not retrievable in abstract or full manuscript form. Two papers were excluded because no data could be provided.
neither from corresponding authors or graphs, bringing the final number of studies to 22 (Fig. 2).

3.2. Risk of bias and quality assessment

No study was judged to have a low risk of bias across all criteria. Fig. 1 summarises the risk of bias assessment results. All trials had unclear or inadequate bias control in one or more of the domains for the assessment of risk of bias. Based on the results, allocation of blinding was the major potential source of bias in this meta-analysis. As well, outcome assessment of sensation and pain was not blinded in 50% of the studies, representing a high risk of bias. However, PEDro scores ranged between 5 and 8 in patient studies (with a mean score of 7.3/11) and between 7 and 8 in healthy volunteer studies (with a mean method score of 7.4/11), which indicate good quality controlled clinical trials. Similarly, the 27-item D&B quality checklist provided a medium-quality mean method score of 17/27 for studies involving healthy participants. Similarly, the 27-item D&B quality checklist provided a medium-quality mean method score of 17/27 for studies involving healthy participants. However, PEDro scores ranged between 5 and 8 in patient studies (with a mean score of 7.3/11) and between 7 and 8 in healthy volunteer studies (with a mean method score of 7.4/11), which indicate good quality controlled clinical trials. Similarly, the 27-item D&B quality checklist provided a medium-quality mean method score of 17/27 for studies involving healthy participants. Table 4 show the PEDro and D&B scores of the included studies.

3.3. Participants in included studies

In total across the included studies, 146 healthy individuals and 276 patients with chronic pain received a-tDCS and sham for VAS measurement. All studies examined the effect of a-tDCS intervention in one or more of the M1, S1 or DLPFC. In the patients with chronic pain, the average VAS was more than 5.

Table 5

tDCS parameters in both healthy (A) and patient (B) groups.

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Type of tDCS</th>
<th>Size of electrode (cm²)</th>
<th>Intensity (mA)</th>
<th>Current density (mA/cm²)</th>
<th>Time of stimulation (min)</th>
<th>Electrode position</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Healthy group</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>5</td>
<td>C3, F3, Oz</td>
</tr>
<tr>
<td></td>
<td>a-tDCS c-tDCS</td>
<td>35</td>
<td>1</td>
<td>0.029</td>
<td>15</td>
<td>C3</td>
</tr>
<tr>
<td>Antal et al. (2008)</td>
<td>a-tDCS</td>
<td>35</td>
<td>1</td>
<td>0.029</td>
<td>15</td>
<td>C3</td>
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<td>Grundmann et al. (2011)</td>
<td>a-tDCS</td>
<td>35</td>
<td>1</td>
<td>0.029</td>
<td>15</td>
<td>C3</td>
</tr>
<tr>
<td>Reidler et al. (2012)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
</tr>
<tr>
<td>Antal et al. (2008)</td>
<td>a-tDCS</td>
<td>35</td>
<td>1</td>
<td>0.029</td>
<td>15</td>
<td>C3</td>
</tr>
<tr>
<td>Csifcsak et al. (2009)</td>
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<td>1</td>
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<td>10</td>
<td>C3</td>
</tr>
<tr>
<td>Ragert et al. (2008)</td>
<td>a-tDCS</td>
<td>20</td>
<td>C3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rogalewski et al. (2004)</td>
<td>a-tDCS</td>
<td>35</td>
<td>1</td>
<td>0.029</td>
<td>7</td>
<td>C4</td>
</tr>
<tr>
<td>Hansen et al. (2011)</td>
<td>a-tDCS</td>
<td>16</td>
<td>1</td>
<td>0.063</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Boggio et al. (2009)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>5</td>
<td>C3, F3, Oz</td>
</tr>
<tr>
<td>B: Patient group</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
</tr>
<tr>
<td>Riberto et al. (2011)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
</tr>
<tr>
<td>Valle et al. (2009)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3 or C4</td>
</tr>
<tr>
<td>Fregni et al. (2006a,b)</td>
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<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
</tr>
<tr>
<td>Roizenblatt et al. (2007)</td>
<td>a-tDCS</td>
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<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
</tr>
<tr>
<td>Mendonca et al. (2011)</td>
<td>a-tDCS</td>
<td>16, 80</td>
<td>2</td>
<td>0.125, 0.0125</td>
<td>20</td>
<td>C3</td>
</tr>
<tr>
<td>Mori et al. (2010)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3 or C4</td>
</tr>
<tr>
<td>Antal et al. (2010)</td>
<td>a-tDCS</td>
<td>16</td>
<td>1</td>
<td>0.063</td>
<td>20</td>
<td>C3</td>
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<tr>
<td>Fregni et al. (2006a,b)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3 or C4</td>
</tr>
<tr>
<td>Fenton et al. (2009)</td>
<td>a-tDCS</td>
<td>35</td>
<td>1</td>
<td>0.029</td>
<td>20</td>
<td>C3 or C4</td>
</tr>
<tr>
<td>Soler et al. (2010)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3 or C4</td>
</tr>
<tr>
<td>Boggio et al. (2009)</td>
<td>a-tDCS</td>
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<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
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<tr>
<td>Dasilva et al. (2012)</td>
<td>a-tDCS</td>
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<td>0.057</td>
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<td>Antal et al. (2011)</td>
<td>a-tDCS</td>
<td>35</td>
<td>2</td>
<td>0.057</td>
<td>20</td>
<td>C3</td>
</tr>
</tbody>
</table>

*1 Abductor digiti minimi.

3.4. Pooled data analysis

For all studies, the standard error (SE) was calculated from the 95% confidence interval of the standardised mean difference and entered into the meta-analysis using the generic inverse variance method. Pre-post a-tDCS studies and active-sham studies were evaluated to assess whether a-tDCS can change STh, PTh, and PL and whether studies using a sham group as a control produced results significantly different from those of pre-post studies. The percentage changes before and after applying a-tDCS and sham a-tDCS were calculated and pooled in meta-analysis.

3.4.1. Effects of a-tDCS on STh in healthy participants

Fig. 3A summarizes the pooled data (percentage of changes) extracted from seven studies on healthy individuals (Antal et al., 2008; Ragert et al., 2008; Csifcsak et al., 2009; Grundmann et al., 2011). As shown, the percentage STh changes were significant for stimulation of M1 with a mean effect size of 19.25%, while a-tDCS of S1 produced no significant mean STh change (P = 0.09). The overall analysis indicated that a-tDCS can change STh significantly (P < 0.001) with an effect size of 13.34%.

Forest plot and meta-analysis results indicated an overall positive mean effect of a-tDCS on STh of 11.22 (Fig. 3B). The subgroup results demonstrated while sham and active a-tDCS generate significantly different STh changes in the M1 subgroup, with a mean effect size of 16.54%, this is not the case in the S1 subgroup.

3.4.2. Effects of a-tDCS on PTh in healthy participants

Seven studies examined the effect of a-tDCS on PTh in healthy individuals (Antal and Paulus, 2008; Csifcsak et al., 2009; Grundmann et al., 2011; Reidler et al., 2012). The stimulation site in two studies was the S1 (Antal et al., 2008; Grundmann et al., 2011; Reidler et al., 2012).
and in the five remaining studies tDCS was applied to the M1 (Fig. 4).

As shown in Fig. 4A, a pooled analysis of eight trials of a-tDCS on the M1 in healthy subjects indicated a significant increase in PTh with a mean effect size of 22.19%. Furthermore, a-tDCS of the S1 significantly increased PTh by a mean of 4.34. The overall effect of a-tDCS on PTh was significant ($P = 0.007$) with the effect size of 16.42% [95% CI: 4.48 to 28.37].

Meta-analysis showed that a-tDCS of both M1 ($P = 0.003$, [95% CI: 22.19 (7.63, 36.76)]) and S1 ($P = 0.02$, [95% CI: 4.34 (0.78, 7.90)]) increased PTh significantly. Although there was no significant difference between sham and active a-tDCS of the S1, analysis of all studies applying a-tDCS onto both the M1 and S1 indicated a positive effect of a-tDCS on PTh ($P = 0.001$, [95% CI: 9.45% (3.70, 15.20)]) (Fig. 4B).
of the S1 might have no effect on sensation (Rogalewski et al., 2004); therefore, any observed effects in STh after a-tDCS of the S1 are probably due to some other mechanism (Dieckhofer et al., 2006; Antal and Paulus, 2008; Ragert et al., 2008). Moreover, other studies reported that rTMS of the somatosensory cortex increased cold perception but not warmth perception (Summers et al., 2004; Oliviero et al., 2005). Sensation of warmth is transmitted via unmyelinated C-fibers and sensation of non-painful cold by small myelinated Aδ fibers (Fuller and Guiloff, 1989), so pooling data for different sensations (cold, warm, vibration, mechanical, etc.) might have altered our results, but the small number of studies made it impossible for us to do so.

4.2. The effect of a-tDCS on PTh in healthy individuals

We hypothesised that PTh is modulated immediately after application of a-tDCS over S1 and M1 in healthy individuals. After a-tDCS of the M1 and S1, significantly increased PTh was observed when compared with the baseline conditions, supporting our hypothesis. Additionally, our comparison of the after-effects of active a-tDCS and sham stimulation of the M1 demonstrated a significant difference in PTh.

These results seem consistent with some PET scan studies that showed that any changes in the resting membrane potential of nerve fibres caused regional cerebral blood flow increase in various structures such as the thalamus, anterior insula, and upper brainstem (Peyron et al., 1995; Garcia-Larrea et al., 1999; Grundmann et al., 2011). Considering the functional connections of motor cortex and deep structures related to pain and sensory processing, a-tDCS may act indirectly on these deep structures to increase PTh (Peyron et al., 1995; Grundmann et al., 2011). The mechanisms behind the efficacy of a-tDCS for PTh remain unclear. Based on the fact that a-tDCS increases corticospinal excitability, it is possible that excitation of neurons under the active electrode may lead to the PTh increase. Other hypothesised mechanisms include long-term potentiation theory (Gamboa et al., 2010) and gating theory (Ziemann and Siebner, 2008), both of which highlight the multiple structures of the central nervous system involved in pain processing (Luedtke et al., 2012; Mylius et al., 2012). Stimulation of M1 is thought to modulate the sensory–discriminative aspects of pain (Porro, 2003). Resting membrane potential of axons might be modulated by a-tDCS, thus TDCS can be explained as mediated primarily by action on M1, but possibly also by action on S1 (Bornhovd et al., 2002; Antal et al., 2008; Mylius et al., 2012). Relevant to this is the finding that rTMS applied at high frequency over M1 improves sensory discrimination as well as providing some pain relief (Passard et al., 2007; Lefaucheur et al., 2012). Also, a-tDCS may impact on intracortical motor circuitry, as suggested by rTMS-induced changes in cortical excitability parameters.

4.3. The effect of a-tDCS on PL in patient group

We hypothesised that PL is modulated immediately after application of a-tDCS over S1 and M1 in patients with chronic pain. Our results support this hypothesis, and the results of two systematic reviews (O’Connell et al., 2011; Luedtke et al., 2012) concluded that a-tDCS is an effective method for reducing pain. Our analysis of the effect of a-tDCS site on PL in patients with chronic pain found that stimulation of both M1 and DLPFC reduces pain in patients with chronic pain. The other interesting finding is, that compared to stimulation of M1, the effect size after applying a-tDCS on DLPFC is bigger. Significant differences in the PL of patients after applying a-tDCS and sham stimulation indicate the efficacy of a-tDCS in pain reduction.

The high level of risk of bias and heterogeneity in the studies we included suggests that more studies with larger sample sizes are required to draw firm conclusions about the effects of a-tDCS, especially of the DLPFC.

In the current study we included different diseases and pathologies (fibromyalgia, spinal cord syndrome, multiple sclerosis, and migraine) in the review and the meta-analysis, which led to substantial heterogeneity. There might be merit in analysing according to condition if sufficient data exist, but there is not an obvious biological reason to predict differential responses.

Although the exact mechanism behind the efficacy of a-tDCS is not clear yet, most of the included studies concluded that the probable mechanism was the changes of resting membrane potential in neurons directly under the active electrode and indirectly in other parts of the pain neuromatrix (like periaqueductal grey, insula, and thalamus) through functional interconnections (Lang et al., 2005). In addition, it has been proposed that TDCS of the M1 can activate descending inhibitory M1-thalamic projections that modulate chronic pain (Fregni et al., 2007). Several rTMS and tDCS studies have shown that stimulation of the DLPFC is associated with improvement of depression (Nitsche et al., 2009, 2012), and thus might have mechanisms of action similar to antidepressants, which are also capable of inducing analgesic effects.

<table>
<thead>
<tr>
<th>Papers</th>
<th>Patients</th>
<th>Stimulation area</th>
<th>Percentages of changes after-before active a-tDCS (mean ± SD)</th>
<th>Percentages of changes after-before sham a-tDCS (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antal et al. (2010)</td>
<td>Trigeminal neuralgia</td>
<td>M1</td>
<td>3.3 ± 1.38</td>
<td>4.8 ± 0.91</td>
</tr>
<tr>
<td>Antal et al. (2011)</td>
<td>Post stroke pain syndrome</td>
<td>M1</td>
<td>8.12 ± 1.22</td>
<td>2.69 ± 0.93</td>
</tr>
<tr>
<td>Boggio et al. (2009)</td>
<td>Refractory orofacial pain</td>
<td>M1</td>
<td>16.7 ± 0.72</td>
<td>5.6 ± 0.54</td>
</tr>
<tr>
<td>Dasilva et al. (2012)</td>
<td>Chronic Neurogenic pain</td>
<td>M1</td>
<td>14.29 ± 2.53</td>
<td>8.23 ± 1.94</td>
</tr>
<tr>
<td>Fenton et al. (2009)</td>
<td>Chronic Migraine</td>
<td>M1</td>
<td>20.31 ± 2.76</td>
<td>10.23 ± 1.99</td>
</tr>
<tr>
<td>Fregni et al. (2006a,b)</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>23.06 ± 3.15</td>
<td>12.17 ± 2.06</td>
</tr>
<tr>
<td>Fregni et al. (2006a,b)</td>
<td>Spinal cord injury</td>
<td>M1</td>
<td>25.83 ± 3.89 29.43 ± 3.96</td>
<td>14.34 ± 2.79 14.57 ± 3.16</td>
</tr>
<tr>
<td>Mendonca et al. (2011)</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>14.74 ± 2.67</td>
<td>6.38 ± 0.95</td>
</tr>
<tr>
<td>Mori et al. 2010</td>
<td>MS</td>
<td>M1</td>
<td>17.48 ± 3.58</td>
<td>8.94 ± 2.05</td>
</tr>
<tr>
<td>Riberto et al. (2011)</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>18.95 ± 3.56</td>
<td>6.95 ± 1.57</td>
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<tr>
<td>Roizenblatt et al. (2007)</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>20.03 ± 4.23 32.84 ± 6.97</td>
<td>9.63 ± 2.18 17.83 ± 5.97</td>
</tr>
<tr>
<td>Soler et al. (2010)</td>
<td>Spinal cord injury</td>
<td>M1</td>
<td>19.39 ± 3.03</td>
<td>3.94 ± 0.92</td>
</tr>
<tr>
<td>Valle et al. (2009)</td>
<td>Fibromyalgia</td>
<td>M1</td>
<td>23.71 ± 2.52 25.81 ± 3.86</td>
<td>13.52 ± 3.01 12.66 ± 2.94</td>
</tr>
</tbody>
</table>

Table 7 Percentage PL changes in patients with chronic pain after applying active a-tDCS and sham TDCS.
4.4. Quality of evidence

Some of the included studies did not clearly report assessor blinding. This could explain the reduced heterogeneity of meta-analyses and the pooled effect size. A recent epidemiological study provided empirical evidence that incomplete blinding in controlled trials that measure subjective outcomes exaggerates the observed effect size by 25% (Wood et al., 2008). This may be the case here, because 2 mA was used in 11 of the 13 included studies of patients with chronic pain and in three of 10 studies of healthy individuals (Table 5). Recently, O’Connell et al. (2012) reported that proper blinding is not possible in a study that uses a current intensity of 2 mA. Though this conclusion was challenged by Russo et al. (2013) and Palm et al. (2013), the implication is that the overall quality of the evidence for the effects of a-tDCS on STh/PTh assessment in healthy individuals and PL assessment in patients with chronic pain should be considered cautiously. Results should be replicated using a current intensity for which blinding is universally accepted as possible.

4.5. Limitations

According to the Cochrane Handbook for Systematic Reviews of Interventions, “potential advantages of meta-analysis include an increase in power, an improvement in precision, the ability to answer question not posted by individual studies, and the opportunity to settle controversies arising from conflicting claims”. That is, establishing clear protocols and inclusion and exclusion criteria can minimise the bias that the reviewer brings to the study. However, we cannot limit the bias that is within the literature itself. There is no doubt that negative findings are less likely to be published and most available studies are fundamentally flawed insofar as they do not include a control group or they do not verify participant blinding (O’Connell et al., 2012).

Other limitations of our study exist. The literature was limited to English-language articles, and most studies used small samples that inflated effect sizes and therefore might affect pooled results. Finally, studies of the effects of tDCS on STh and PTh used different types of sensation modalities and methods. As a result, because of small number of studies investigated the effects of a-tDCS on STh and PTh, we were not able to study the effect of a-tDCS on each stimulation method separately.

It is worth noting that the present study limited to immediate after-effects of a-tDCS not long-lasting effects. Due to limited number of included studies and mismatched measurement time-points, it was impossible to evaluate long-lasting after-effects of a-tDCS based on the site of stimulation.

4.6. Areas for future research

The results of our review indicate that a-tDCS of the M1 increases PTh in healthy individuals, and that a-tDCS of both the M1 and the DLPFC reduces PL of patients with chronic pain. An obvious future direction is to perform similar studies by testing the effects of cathodal tDCS (c-tDCS). The studies conducted in healthy subjects and patients with chronic pain thus far have been limited to a single a-tDCS session of approximately 20 min. It is
possible that longer application time or multiple applications could significantly increase pain thresholds or reduce pain levels (Nitsche et al., 2005; Furubayashi et al., 2008). Moreover, no study to date has optimized parameters regarding the analgesic effects of a-tDCS on both healthy and pain patient groups. Based on the fact that c-tDCS can suppress M1 excitability for up to 60 min after stimulation (Nitsche and Paulus, 2000; Rainville, 2002; Zaehle et al., 2011; Di Lazzaro et al., 2012), research focusing on the analgesic effects of c-tDCS could develop a more efficient method for pain treatment. Finally, since there are complicated relationships between different parts of the brain related to pain processing, subsequent research could aim to find the best stimulation sites and develop an efficient tDCS protocol to reduce pain.

Regarding the importance of therapeutic effects of tDCS in pain treatment, further investigation is required to evaluate the long-term effects of a-tDCS on STh/PTh in healthy individuals and PL in patients with chronic pain.

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References


Fig. 4. Forest plot of comparison; (A) after-effects of a-tDCS compared to baseline value, (B) after-effects of a-tDCS compared to sham stimulation. Outcome: percentages of self-reported PTh changes, subgroup analysis: M1 and S1.

Fig. 5. Forest plot of comparison; (A) after-effects of a-tDCS compared to baseline value, (B) after-effects of a-tDCS compared to sham stimulation. Outcome: percentages of self-reported PL changes, subgroup analysis: M1 and DLPFC.


Scaparza C, Sartori G, De Simone MS, Mecchi A. When the single matters more than the group: very high false positive rates in single case Voxel Based Morphometry. Neuroimage 2013;70:175–88.


