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

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HIGHLIGHTS

- Anodal tDCS (a-tDCS) of the primary motor cortex increases sensory and pain threshold in healthy individuals.
- a-tDCS of the primary sensory cortex increases pain threshold significantly.
- a-tDCS of both primary motor cortex and dorsolateral prefrontal cortex decreases pain level in patients with chronic pain.

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

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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) (Lefaucheur 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; Csifcsak 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 M1in 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 Woolf, 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).