Chapter 37

Non-invasive Transcranial Direct Current Stimulation for the Study and Treatment of Neuropathic Pain

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Abstract

In the last decade, radiological neuroimaging techniques have enhanced the study of mechanisms involved in the development and maintenance of neuropathic pain. Recent findings suggest that neuropathic pain in certain pain syndromes (e.g., complex regional pain syndrome/reflex sympathic dystrophy, phantom-limb pain) is associated with a functional reorganization and hyperexitability of the somatosensory and motor cortex. Studies showing that the reversal of cortical reorganization in patients with spontaneous or provoked pain is accompanied by pain relief stimulated the search for novel alternatives how to modulate the cortical excitability as a strategy to relieve pain. Recently, non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) were proposed as suitable methods for modulation of cortical excitability. Both techniques (TMS and tDCS) have been clinically investigated in healthy volunteers as well as in patients with various clinical pathologies and variety of pain syndromes. Although there is less evidence on tDCS as compared with TMS, the findings on tDCS in patients with pain are promising, showing an analgesic effect of tDCS, and observations up to date justify the use of tDCS for the treatment of pain in selected patient populations. tDCS has been shown to be very safe if utilized within the current protocols. In addition, tDCS has been proven to be easy to apply, portable and not expensive, which further enhances great clinical potential of this technique.

Key words: Transcranial direct current stimulation (tDCS), Neuropathic pain, Pain management

1. Introduction

In the last decade, radiological neuroimaging techniques have enhanced the study of mechanisms involved in the development and maintenance of neuropathic pain. Recent findings suggest that pain in certain neuropatic pain syndromes (e.g., complex regional pain syndrome/reflex sympathic dystrophy [CRPS/RSD], fibromyalgia, phantom-limb pain) is assoliated with functional reorganization of the somatosensory and motor cortices (1–9).

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Cortical reorganization involves two main phenomena: (1) changes in somatotopic organization and (2) changes in excitability of the somatosensory and motor cortices. The observation that the reversal of cortical reorganization in patients with spontaneous or provoked pain is accompanied by pain relief (1–3) further stimulated the search for novel alternatives to modulate the cortical excitability as a strategy to relieve pain. In early studies, pain relief was achieved using invasive electrical stimulation with electrodes implanted over the motor cortex (10–12). Although promising results were reported with this approach, due to the invasive nature of this procedure, a clinical use of this technique as well as research studies remained to very specific patiem-populations limited. Recently, non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) were proposed as suitable methods for modulation of cortical excitability in patients with certain types of pain. Both TMS and tDCS have been studied in healthy volunteers (13–17), patients with various disorders (18–26), and in various pain syndromes (27–35). Although there is less evidence on the use of tDCS, as compared to TMS, the findings are very promising, and the observations up to date justify the use of tDCS for the treatment of pain in selected patient populations (27, 30, 34–39). The findings on tDCS safety suggest that the application of tDCS to motor and non-motor cortical areas is associated with relatively minor side effects if the safety recommendations are followed (40–53). In addition, tDCS has been proven to be easy to apply, portable, and not expensive, which further enhances great clinical potential of this technique.

This protocol and procedure describe the use of tDCS for the study and alleviation of spontaneous chronic pain and does not apply to experimentally induced or spontaneous acute pain.

2. Materials

1. tDCS device Phoresor® II Auto, Model No. PM850 or PM950 (IOMED, Salt Lake City, UT), consisting of the main battery-operated unit and a twin wire to connect the unit with electrodes (Fig. 1).
2. Two large saline-soaked sponge-electrodes (contact area 25 or 36 cm^2) and two cables, both with the ends “crocodile to banana”.
3. An equipment for determining the proper position of the electrodes. Either an automated visual navigation system can be used, or the position can be determined manually using the 10–20 International system of the electroencephalographic electrode placement.

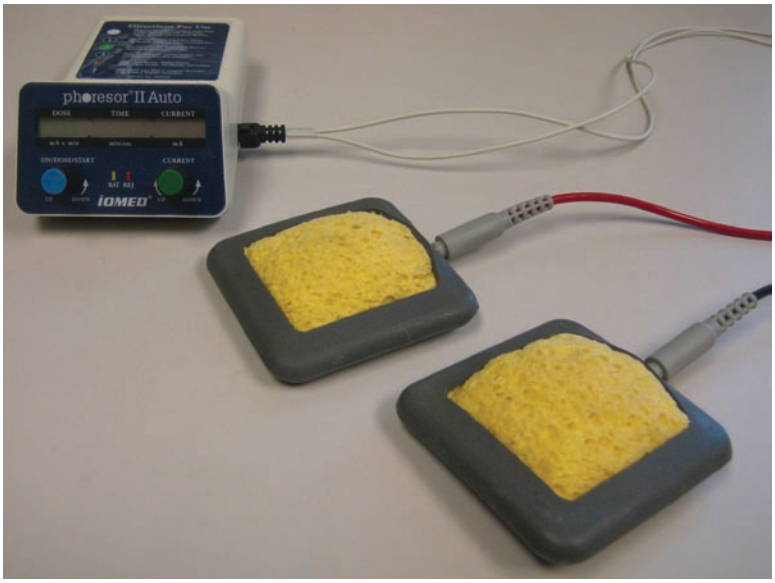

Fig. 1. The tDCS device. The tDCS device consists of the main battery-operated unit and two larger saline-soaked electrodes

4. Normal saline (9 g/liter).
5. Two elastic bands, medical tape, flexible plastic meter.

3. Methods

tDCS is based on influencing neuronal excitability and modulating the firing rates of individual neurons by a low amplitude direct current which is delivered non-invasively through the scalp to the selected brain structures (54, 55). The nature of tDCS-induced modulation of cortical excitability depends on polarity of the current. Animal studies suggest that cathodal stimulation decreases the resting membrane potential and therefore hyperpolarizes neurons, whereas anodal stimulation causes depolarization by increasing resting membrane potentials and spontaneuous neuronal discharge rates (56–58). Generally, anodal tDCS increases cortical excitability, while cathodal tDCS decreases it (59, 60).

Anodal tDCS increases cortical excitability by reducing intracortical inhibition and enhancing intracortical facilitation. Cathodal tDCS diminishes excitability by reducing intracortical facilitation during stimulation and additionally by increasing intracortical inhibition after stimulation (54, 55, 60). Some of tDCS-induced changes occurs immediately during the

stimulation (so called intra-tDCS changes), while others occur later as short-lasting and long-lasting after-effects.

The intra-tDCS effects which elicit no after-effects can be induced by a short (seconds) single application of tDCS. As suggested by recent pharmacological studies, intra-effects depend on the activity of sodium and calcium channels but not on efficacy changes of NMDA and GABA receptors, and thus are probably generated solely by polarity specific shifts of resting membrane potential (61–64). The intra-tDCS effect of cathodal tDCS is reduction of intracortical facilitation, while anodal tDCS has no intra-effect on intracortical facilitation or inhibition; all effects of anodal stimulation occur later as after-effects.

The short-lasting effects lasts 5–10 min after the end of stimulation and can be induced by application of 7 min of 1 mA tDCS, while to obtain long-lasting effects (about 1 h) at least 13 min of 1 mA tDCS is needed. As shown by Nitsche and colleagues (63), the after-effects critically depend on membrane potential changes, but have been demonstrated to involve also modulations of NMDA receptors efficacy (61). After-effects of anodal tDCS involve reduction of intracortical inhibition and enhancement of intracortical facilitation, while cathodal tDCS after-effect represent enhancement of intracortical inhibition (54, 55, 60).

Although data on the use of tDCS to alleviate pain are limited and large controlled studies need to be conducted, the findings (27, 30, 34–38) show that the anodal tDCS delivered over the motor cortex in patients with chronic pain can induce significant pain relief, as compared with baseline prior the tDCS and/or with a "placebo" sham tDCS.

Analgesic effects induced by tDCS outlast the period of stimulation and are cumulative, transient and site-specific.

Although the exact mechanisms responsible for underlying pain relief induced by the motor cortex stimulation have not yet been fully elucidated, some results suggests that the decrease in pain sensations that follows the motor cortex stimulation might be at least in part linked to changes in the thalamic activity (65, 66). PET scans performed in patients with neuropathic pain after motor cortex stimulation showed significant increase in cerebral blood flow in the ventral-lateral thalamus, medial thalamus, anterior cingulate/orbitofrontal cortex, anterior insula and upper brainstem (65). All of these areas are known to be involved in various mechanisms of transmission of pain. It is reasonable to speculate that the activation of the motor cortex in the hemisphere contralateral to the painful limb may trigger thalamic activity directly via cortico-thalamic projections, and this in turn might modulate the ascending nociceptive pathways, such as spinothalamic tract, which is considered to be the predominant pain-signaling pathway.

Further, there is an increasing evidence suggesting that changes in cortical excitability induced by motor cortex stimulation may be partially linked to the activity of dopaminergic neurons (67, 68). Recent insights have demonstrated a central role for dopaminergic neurotransmission in modulating pain perception and natural analgesia within supraspinal regions, including the basal ganglia, insula, anterior cingulate cortex, thalamus and periaqueductal gray, as well as in descending pathways (69). Decreased level of dopamine likely contributes to the painful symptoms that frequently occur in Parkinson's disease, and abnormalities in dopaminergic transmission have been objectively demonstrated in painful clinical conditions such as fibromyalgia (70).

Safety of tDCS has been evaluated in animal studies (41–44), as well as human studies (45–53, 71) involving healthy volunteers, and patients with various disorders. A recent study (71) looked at the prevalence of side-effects in a cohort of 102 subjects with a total of 567 tDCS sessions in which electrical current of 1 mA was applied over the primary motor cortex as well as other cortical areas (somatosensory, visual, dorsolateral prefrontal, parietal, and auditory cortex) (71). The pool of participants consisted of healthy subjects (75.5%), migraine patients (8.8%), post-stroke patients (5.9%), and tinnitus patients (9.8%). Results showed that during tDCS the most common reported side effect was a mild tingling sensation directly under the electrode (70.6%), a light itching sensation under the electrode (30.4%), and moderate fatigue (35.3%). In addition, headache (11.8%), nausea (2.9%), and insomnia (0.98%) were also reported. The overall findings on tDCS safety suggest that the application of tDCS to various cortical areas *is not* associated with occurrence of any serious side-effects.

The description of the procedure as appears below, relates to the use of anodal tDCS for alleviation of spontaneous chronic pain, and does not apply to experimentally induced- or spontaneous acute pain, or to the tDCS treatment of any other medical condition.

1. Using an elastic band, two saline-soaked sponge-electrodes are placed on the subject's head as follows: the anode over the motor cortex (see Note 1) of the hemisphere contralateral to the affected part of the body; the cathode over the supraorbital region of the ipsilateral hemisphere.
2. The area of the motor cortex can be determined either using the automated navigational system, or manually as the position of C4 (on the right hemisphere) or C3 (on the left hemisphere) (Fig. 2). C3/C4 respectively are located 7 cm from Cz point.
3. The main tDCS unit gets connected with electrodes.

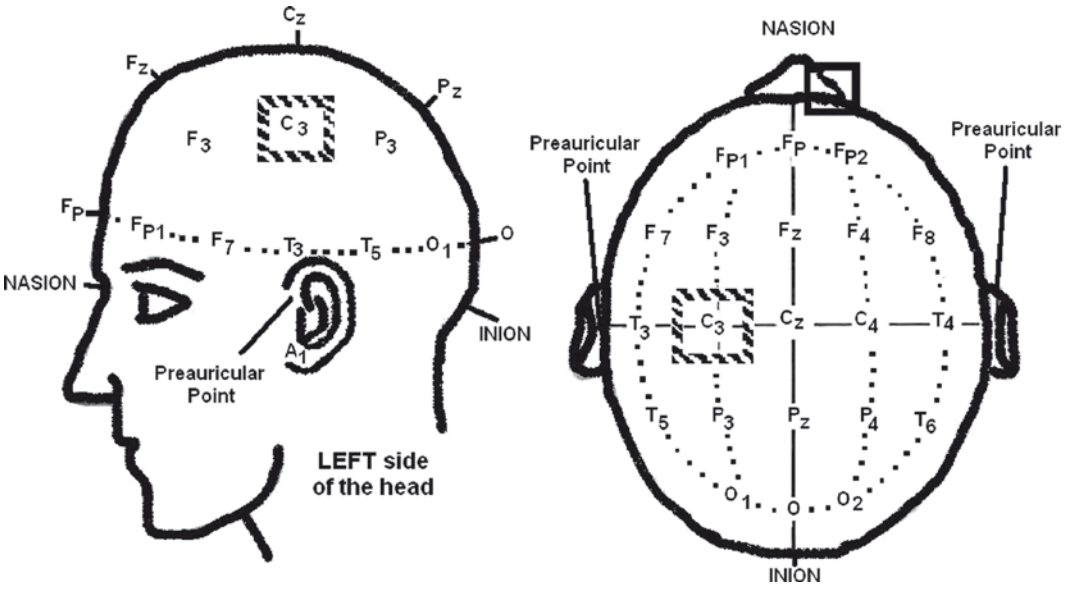

Fig. 2. The 10-20 EEG International System used for a manual positioning of the tDCS electrodes. To alleviate chronic spontaneous pain, the anode is placed at the position of C3 or C4 which lies in the area of the motor cortex on the left and right hemisphere respectively. In general, the anode has to be placed on the hemisphere contralateral to the affected part of the body, while the cathode is placed over the supraorbital region ipsilateral to the affected side

4. Desired intensity of the stimulation and time (see Note 2) is manually pre-set on the display. After the safety check (the right position of the electrodes, cable-connections, parameters on the display), the main unit is switched on.
5. The intensity of current increases automatically in the ramp manner over several seconds until reaching desired intensity.
6. At the end of stimulation, the intensity of the current gradually decreases to zero and the unit visually and acoustically signals the end of stimulation.
7. The tDCS procedure is usually delivered as a block of treatment, i.e., repeated on several consecutive days (see Note 3).
8. For long-term pain control, the block of tDCS treatment can be repeated (see Note 4).

4. Notes

1. Analgesic effects are site-specific. In a study by Roizenblatt and colleagues (30), thirty-two fibromyalgia patients were randomized into three arms to receive either sham or anodal tDCS (at the intensity of 2 mA for 20 min) delivered either over the primary motor cortex, or the dorsolateral prefrontal

cortex (DLPFC), on five consecutive days. The results indicated that neither sham nor real tDCS anodal stimulation over DLPFC produced significant pain relief. The stimulation over the primary motor cortex was the only parameter associated with a significant reduction of pain, with 59% pain relief after the last session. Up to date, published sham-controlled studies in population with chronic pain utilized the anodal tDCS delivered over the motor cortex. However, there is some preliminary evidence (39, 72) that analgesic effect can also be induced by targeting the somatosensory cortex provided that the *cathodal* stimulation is used.

2. The parameters utilized in clinical and research trials with tDCS in healthy volunteers and patients with various diagnoses vary highly and include differences in the position of the electrodes, polarity of the current (anodal or cathodal), intensity, and duration of the stimulation. In the studies using tDCS in patients with spontaneous chronic pain (27, 30, 34–38), anodal tDCS up to the intensity of 2 mA for up to 20 min over the motor cortex on up to five consecutive days has been safely applied, without eliciting any serious adverse effects.
3. The analgesic effects of tDCS are cumulative. Several independent observations indicated that repeated tDCS sessions on several (five) consecutive days can yield significantly better pain relief than a single application (27, 30, 35, 36). The findings showed that pain intensity after tDCS on Day-5 was substantially lower than pain intensity after Day-1 as compared to Baseline, and significant difference was also observed between pain intensity on Day-1 and Day-2 as compared with Baseline. For example, in the study in patients with central pain due to spinal cord injury (27), the results showed non-significant pain relief after Day-1, while after Day-2 the decrease in pain ratings reached significance $p<0.05$, and and after day 5 $p<0.001$, (27).
4. Analgesic effects of tDCS outlast the tDCS session but diminish with time. Evidence up to date in concordance indicate that although the pain relieving effect of tDCS outlasts the period of stimulation, the effect is not permanent (27, 30, 35–38). For example, in the study of patients with central pain due to spinal cord injury, the mean pain intensity after the active tDCS decreased from 6.2 at the baseline to 2.6 at the end of the fifth tDCS session, and the magnitude of this effect diminished somewhat at the follow up 16 days later (mean VAS pain intensity 3.9), but was still significant when compared with baseline (27). Similarly, in patients with fibromyalgia pain relief lasts beyond the fifth session, and although the effect diminished with time, three weeks after the last session, the pain relief was still highly significant when compared to baseline values (30, 36).

In a case obervation (45) of a patient with CRPS/RSD who received tDCS repeatedly in five blocks (each block consisting of five consecutive days) in "as needed" regimen, the duration of pain relief ranged between 3 and 11 weeks (35). No analgesic tolerance (a phenomenon often observed during opioid treatments, when the analgesic response to a specific dose declines with repeated use of the drug) was observed in the patient.

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