Chapter 8
Transcranial Direct Current Stimulation

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Abbreviations

DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
M1	Motor cortex
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VEP	Visual-evoked potential

8.1 Introduction and Rationale

Migraine is the most prevalent form of disabling headache. For clinicians, treating migraine with the available preventative pharmacological approaches raises some major problems, as the average efficacy rate of any prophylactic drugs hardly exceed 50%, and almost all pharmacological treatments used in migraine prophylaxis are associated with cumbersome and sometimes intolerable adverse effects. As a matter of fact, other preventative strategies are needed. Pointing to obtain a better tolerability of treatments and a superior compliance to them with respect to the approaches commonly used, numerous non-pharmacological treatments for migraine have been tested in recent years. Among them, noninvasive neuromodulation methods appear as a promising approach, as they are much better tolerated and accepted than drugs or invasive techniques, and they have very few contraindications, thus do not need to be restricted to limited subgroups of patients. In this chapter, we will focus on

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transcranial direct current stimulation (tDCS), an application of neuromodulation methods aimed to modify cortical excitability. In comparison to other cortical neurostimulation techniques, such as transcranial magnetic stimulation (TMS), tDCS offers peculiar advantages: it influences larger regions of the cortex than TMS, it can modulate cortical activities without causing action potentials, and it produces fewer physiological artifacts than TMS, such as muscle twitches and auditory noise. Moreover, opposite effects on cortical activation can be obtained when inverting anodal (excitability enhancer) and cathodal stimulation (excitability depressor). Finally, it is cheaper and easier to apply than TMS, and portable devices are available.

The rationale for using tDCS as a potential approach to migraine prophylaxis is based on the fact this method may act directly on some pathophysiological aspects of migraine, such as the interictal abnormal cortical responsivity and the consequent abnormal corticothalamic information processing, by normalizing them [1].

In normal subjects, the cortical responses to prolonged repetitive sensory stimuli become progressively lower with respect to the starting of stimulation (see [2] for a review). This phenomenon is usually called “habituation.” By contrast, in migraine patients, the initial cortical responses to repetitive sensory stimulation are low but tend to increase in amplitude along that the stimulation is prolonged, producing a response pattern called “deficit of habituation” or, sometimes, “potentiation.” This happens only between attacks because during the pain phase and in the days immediately before and after the attack, the response pattern is like that found in healthy subjects [3]. Interictal habituation deficit has been observed for cortical responses to all sensory modalities. Abnormal cortical responsivity was also testified by EEG hypersynchronization during repetitive photic stimulation. It has been hypothesized that this abnormal pattern of cortical responses to external repetitive solicitations may be caused by an interictal decreased preactivation level of sensory cortices in migraine patients and that this defect could be the consequence of an abnormal rhythmic activity between thalamus and cortex, namely thalamocortical dysrhythmia [4]. Interestingly, tDCS can restore the normal habituation pattern both for visual-evoked potentials when applied as cathodal tDCS over the visual cortex [5] and for somatosensory-evoked potential when applied as anodal tDCS over the left temporal pole [6].

tDCS appears thus as a promising tool to achieve protection from migraine attacks: it could act directly on the peculiar neurophysiological aspects which differentiate the migraine brain from a healthy brain. It offers the possibility to obtain modulation by different polarities and on different cortical areas so that many combinations of stimulation settings could be tested, searching for the one which may produce the best outcome for migraine prophylaxis.

At present, few randomized sham-controlled trials are available on tDCS for migraine prevention. Different stimulation protocols have been proposed, but results obtained are quite interesting, although the largest part of these studies implicated a small number of patients.

8.2 Technical Aspects

tDCS is obtained when a constant current is passed from one electrode (the anode, with positive charge) to the other (the cathode, with negative charge) over a short period of time (usually 8–20 min). The active electrode (anodal or cathodal according to the chosen type of stimulation) has always to be applied to the scalp, above the region targeted for stimulation, identified usually by the 10–20 EEG system; the reference electrode could be placed on the scalp (contralaterally to the active electrode or on the vertex) or on an extracranial region (contralateral shoulder or arm). The intensity of stimulation is usually kept below the threshold of perception, and the density of stimulation (mA/cm^2) shall always be kept under the threshold of possible tissue damages. Portable devices are available to be used by patients, which is particularly useful when multiple daily sessions are needed. However, patients wanting to use these devices in a domestic setting should be carefully trained to the appropriate use of them, to the identification of the target cortical regions, and to the parameters to be used.

As anticipated, anodal and cathodal stimulation produces different effects on human cortical areas: when applied on the motor cortex, anodal stimulation induces cortical hyperexcitability, whereas cathodal stimulation decreases cortical excitability [7–9]. Visual cortex seems as well to be influenced in an opposite way by anodal and cathodal stimulations [10, 11]. Interestingly, tDCS can also influence regions functionally connected to the stimulated area, which is relevant for studies investigating brain networks and connectivity [12].

tDCS is supposed to modulate synaptic activity via neurotransmitters, in particular GABA, glutamate, acetylcholine, serotonin, and dopamine. Many factors may influence tDCS activity on cortical excitability: among them, the intensity of stimulation, individual differences in current flow, concomitant activity of cortical region stimulated, and drugs that are supposed to act on modulation of neuronal membrane potentials [13].

8.3 tDCS in Migraine Prophylaxis

8.3.1 Visual Cortex

It was demonstrated that visual-evoked potential (VEP) habituation in migraine patients can be restored for long periods after five consecutive daily sessions of activating repetitive TMS over the visual cortex [14]. According to these findings and following the hypothesis that the correction of the sensory processing defect may reflect a virtuous re-modulation of the brain networks implicated in migraine pathophysiology, visual cortex was one of the first cortical targets for exploring the potential beneficial activity of tDCS stimulation in migraine prevention.

However, whether tDCS should increase or decrease visual cortical excitability to correct the sensory-processing defect is a matter of discussion. Using TMS over primary visual cortices in migraine patients, some investigations showed a reduced threshold to elicit phosphenes with respect to healthy subject, thus a cortical hyperexcitability, which is the opposite of what was suggested by VEP habituation studies. However, these findings were not replicated in other studies (see [15] for a review), and magnetophosphene thresholds are not correlated to the deficient VEP habituation patterns in migraine patients, suggesting that they measure different aspects of cortical excitability: phosphene thresholds are likely to express punctual normal measures of the cortical activation threshold, whereas VEP habituation reflects a dynamic response pattern to repeated stimuli [16] (Table 8.1).

In fact, in two sham-controlled studies for migraine prevention, where repeated cathodal tDCS, aimed to reduce cortical excitability, was applied over the visual cortex, no differences were found in the clinical outcome between verum and sham. In the first one [17], a randomized sham-controlled trial, 26 migraine patients (12 without aura, 14 with aura) were enrolled. The verum was a cathodal constant current of 1 mA intensity applied for 15 min over Oz; the sham stimulation was obtained by the same protocol, but the stimulator was switched off after 30 s. Sessions were daily for 3 days/week. During the first 3 weeks, all the patients underwent sham stimulation, while during the following 3 weeks, 13 patients had verum and 13 still sham. Comparing the outcomes, no differences were found between groups about frequency, duration, and migraine-related days, but in the verum group, a slight reduction of pain intensity was observed. A similar protocol (1 daily session, 3 days/week) was used in the second randomized, double-blinded, parallel group-controlled, pilot trial [20]. In this study, ten migraineurs were treated for 4 weeks with 20-min sessions of cathodal tDCS over the visual cortex and compared with five patients assigned to sham stimulation; no difference was found between groups in frequency, duration, or intensity of attacks besides a slight reduction in painkiller use in the verum group. Only one investigation proposed anodal tDCS instead of cathodal, with the objective to increase the visual cortex preactivation level. In this open uncontrolled "proof-of-concept" study [5], ten migraineurs without aura underwent daily sessions (twice a week) for consecutive 8 weeks. Anodal tDCS was a 15-min stimulation (intensity: 1 mA) over the visual cortex. During the second month of treatment, there was a significant reduction in attack frequency (−38%), migraine days (−48%), attack duration (−60%), and acute drug intake (−28%) in comparison with the baseline. Unfortunately, in this study—uncontrolled and open—authors also included some migraineurs taking preventative medications; thus, these results need to be confirmed in a large randomized sham-controlled trial.

Table 8.1 tDCS studies as prophylactic treatment of migraine

Authors	Participants	Study	Treatment	Results
Antal et al. [17]	MO = 12 MA = 14	Randomized sham-controlled trial	Cathode over V1	No reduction was observed in attacks frequency in both groups (tDCS and sham) despite patients under real stimulation experienced a tendency to a reduction in the number of migraine-related days, attacks duration, and pain intensity
Dasilva et al. [18]	CM = 13	Randomized sham-controlled trial	Anode over M1	More significant reduction in pain intensity after 4 months with tDCS than sham
Auvichayapat et al. [19]	M = 37	Randomized sham-controlled trial	Anode over M1	Significant more reduction in attacks frequency, number of abortive medications, and pain intensity with tDCS than sham
Viganò et al. [5]	MO = 10	Open-label study	Anode over V1	Reduction in attacks frequency, migraine days, attack duration, and acute treatment intake after 2 months of tDCS
Rocha et al. [20]	M = 15	Randomized, double-blinded, parallel group-controlled, pilot trial	Cathode over V1	No reduction was observed in attacks frequency, pain intensity, and duration in patients under real tDCS as compared with patients under sham stimulation. A significant reduction of number of acute drugs intake was observed with tDCS, but with sham
Przeklasa-Muszyńska et al. [21]	MO = 12 MA = 18	Open-label study	Anode over M1	The consumption of analgesics and triptans, pain intensity, attacks duration, and the number of headache days decreased after tDCS
Andrade et al. [22]	M = 13	Pilot, double-blind, placebo-controlled, randomized trial	Anode over M1 or DLPFC	Group under DLPFC stimulation exhibited a better clinical performance compared with groups under M1 and sham stimulations. On intragroup comparison, groups DLPFC and M1 exhibited a greater reduction in headache impact and pain intensity and a higher quality of life after real treatment. No significant change was found in the group under sham stimulation

CM chronic migraine, *DLPFC* dorsolateral prefrontal cortex, *M* migraineurs patients, *MA* migraine with aura, *MO* migraine without aura, *tDCS* transcranial direct current stimulation

8.3.2 Other Cortical Areas

Starting from the observation that chronic migraine is associated to structural and functional abnormalities in the pain-related networks [23], in a randomized sham-controlled, double-blinded study, tDCS was applied with anode electrode placed over the motor cortex (contralateral to the most painful side) and the cathode placed over the contralateral supraorbital area. tDCS was delivered in ten 20-min sessions over 4 weeks; the verum group (ten patients) received current of 2 mA, whereas in the sham group (five patients), the same intensity was delivered only in the first 30 s. Although only a trend for reduction of headache intensity was found in the active group at the end of the study, a 4-month follow-up revealed a significant improvement in subjective pain perception and a trend for reduced attack duration [18]. An identical protocol was performed on 50 women suffering from episodic migraine (30 without aura and 20 with aura). In the verum group (30 patients), a significant reduction in headache duration, attack frequency, and pain intensity was observed at the end of the study [21].

In another sham-controlled study where tDCS was applied by anodal stimulation over the motor cortex, 37 episodic migraine patients were treated with anodal ($N = 20$) or sham ($N = 17$) stimulation (intensity: 1 mA) for 20 min over 20 consecutive days. In the verum group, attack frequency and abortive medications were significantly reduced at week 4 and 8 after treatment, and the pain intensity was significantly reduced at weeks 4, 8, and 12 [19]. In a very recent sham-controlled randomized investigation, a small group of 13 chronic medical refractory migraine patients received tDCS over the motor cortex (M1) or the left dorsolateral prefrontal cortex (DLPFC). They underwent 12 20-min sessions of anodal tDCS (intensity of 2 mA) for 1 month. After the treatment, both the M1 group (six patients) and the DLPFC group (four patients) had a significant reduction of pain intensity and headache impact with respect to the sham group (three patients), with a better outcome in the DLPFC-treated patients [22].

8.4 Conclusions

Transcranial direct current stimulation (tDCS) seems to disclose promising horizons in headache treatment. Although multiple repetitive sessions of stimulation are needed to obtain positive outcomes, the devices are not expensive and are portable so that patients, when appropriately trained, may be able to treat themselves also in a domestic setting. Controlled studies based on the rationale that in migraine the cerebral cortex is hyperexcitable, and thus using cathodal tDCS inhibition, found no significant therapeutic effect. By contrast, when activation of the visual cortical areas was obtained by anodal tDCS, a significant improvement was obtained in migraine attack frequency and duration [5]. Unfortunately, this protocol was not yet proposed in a sham-controlled randomized trial, which could confirm this beneficial effect.

Similarly, anodal tDCS applied over other cortical areas, mainly the primary motor cortex but also DLPFC, seems to be promising in episodic and chronic migraine prevention; some small placebo-controlled trials are available to sustain these findings, which should be replicated in larger groups of patients.

In summary, although at the present tDCS cannot yet be proposed as an established treatment for migraine prophylaxis, it offers many future opportunities to improve migraineurs' quality of life, and most of them only need to be explored.

References

1. Coppola G, Di Lorenzo C, Serrao M, et al. Pathophysiological targets for non-pharmacological treatment of migraine. Cephalalgia. 2016;36:1103–11.
2. De Tommaso M, Ambrosini A, Brighina F, et al. Altered processing of sensory stimuli in patients with migraine. Nat Rev Neurol. 2014;10(3):144–55. https://doi.org/10.1038/nrneurol.2014.14.
3. Judit A, Sandor PS, Schoenen J. Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. Cephalalgia. 2000;20:714–9.
4. Coppola G, Ambrosini A, Di Clemente L, et al. Interictal abnormalities of gamma band activity in visual evoked responses in migraine: an indication of thalamocortical dysrhythmia? Cephalalgia. 2007;27:1360–7.
5. Viganò A, D'Elia TS, Sava SL, et al. Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. J Headache Pain. 2013;14:23.
6. Cortese F, Pierelli F, Bove I, et al. Anodal transcranial direct current stimulation over the left temporal pole restores normal visual evoked potential habituation in interictal migraineurs. J Headache Pain. 2017;18:70.
7. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
8. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57:1899–901.
9. Pellicciari MC, Brignani D, Miniussi C. Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. NeuroImage. 2013;83:569–80.
10. Antal A, Kincses TZ, Nitsche MA, et al. Manipulation of phosphene thresholds by transcranial direct current stimulation in man. Exp Brain Res. 2003;150:375–8.
11. Antal A, Kincses TZ, Nitsche MA, et al. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Vis Sci. 2004;45:702–7.
12. Turi Z, Paulus W, Antal A. Functional neuroimaging and transcranial electrical stimulation. Clin EEG Neurosci. 2012;43:200–8.
13. Di Lazzaro V, Rothwell J, Capogna M. Noninvasive stimulation of the human brain: activation of multiple cortical circuits. Neurosci. 2018;24(3):246–60.
14. Bohotin V, Fumal A, Vandenheede M, et al. Effects of repetitive transcranial magnetic stimulation on visual evoked potentials in migraine. Brain. 2002;125:912–22.
15. Brigo F, Storti M, Nardone R, et al. Transcranial magnetic stimulation of visual cortex in migraine patients: a systematic review with meta-analysis. J Headache Pain. 2012;13:339–49.
16. Ambrosini A, Iezzi E, Perrotta A, et al. Correlation between habituation of visual-evoked potentials and magnetophosphene thresholds in migraine: a case-control study. Cephalalgia. 2016;36:258–64.

17. Antal A, Kriener N, Lang N, et al. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia. 2011;31:820–8.
18. Dasilva A, Mendonca ME, Zaghi S, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache. 2012;52:1283–95.
19. Auvichayapat P, Janyacharoen T, Rotenberg A, et al. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. J Med Assoc Thail. 2012;95:1003–12.
20. Rocha S, Melo L, Boudoux C, et al. Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: a pilot randomized controlled trial. J Neurol Sci. 2015;349:33–9.
21. Przeklasa-Muszyńska A, Kocot-Kępska M, Dobrogowski J, et al. Transcranial direct current stimulation (tDCS) and its influence on analgesics effectiveness in patients suffering from migraine headache. Pharmacol Reports. 2017;69:714–21.
22. Andrade SM, de Brito Aranha REL, de Oliveira EA, et al. Transcranial direct current stimulation over the primary motor vs. prefrontal cortex in refractory chronic migraine: a pilot randomized controlled trial. J Neurol Sci. 2017;378:225–32.
23. Sprenger T, Borsook D. Migraine changes the brain: neuroimaging makes its mark. Curr Opin Neurol. 2012;25:252–62.