The efficacy of tDCS in the treatment of migraine: A review.

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Abstract

This review summarizes the existing available data on the use of transcranial Direct Current Stimulation (tDCS) as a treatment for migraine symptoms both with and without aura. 27 studies were examined and 5 were included in the review (which satisfied the inclusion criteria, i.e., duration of tDCS, intensity of stimulation, type of stimulation and stimulated cerebral area). The visual cortex was stimulated in 4 of the 5 analyzed studies. All these studies reported a 1 mA current flowing (anodic stimulation), with a duration of 15-to-20 minutes but not the same montage protocol. The sessions were then repeated 2-4 times a week, for a variable period of 4-8 weeks. The other study adopted a cathodic stimulation on the primary motor cortex with an intensity of 2 mA. Both anodic and cathodic stimulations on the visual cortex provided important results: repeated series of preventive anodic stimulations resulted in a decrease in the regularity of migraine attacks, duration and pain perceived by the patient. The study about the stimulation of the motor cortex pointed out a decrease in the regularity and duration of attacks. Overall, the tDCS can be considered as a useful instrument, capable of bringing benefits to patient suffering from migraine; however, the duration of the obtained benefits was limited in all the cases reported and the size of sample was too small. Further studies are therefore needed to better comprehend the mechanisms involved in the pathogenesis of migraine symptoms.

Keywords: Migraine, tDCS.

Abbreviations: CSD: Cortical Spreading Depression; CZOZ: Electrode position according to 10-20 EEG System; EEG: Electroencephalography; fMRI: Functional Magnetic Resonance Imaging; Hz: Hertz; mA: Milliampere; NIBS: NonInvasive Brain Stimulation; PET: Positron Emission Tomography; M1: Primary Motor Cortex; V1: Primary Visual Cortex; rTMS: Repetitive Transcranial Magnetic Stimulation; tDCS: Transcranial Direct Current Stimulation; TMS: Transcranial Magnetic Stimulation.

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Introduction

Background of the study

Migraine is a complex and heterogeneous disorder, in which environmental and genetic factors interact to generate dysfunctional behaviors at different levels of the central nervous system. These phenomena cause a series of heterogeneous clinical symptoms, whose dynamics are characterized by a cyclic ictal and interictal pattern and by recurring and repetitive attacks [1]. Controversial data emerged from studies carried out on migraine patients; however, from a careful review of the literature it could be inferred that migraine is characterized by a cortico-cortical failure affecting all sensory areas [2,3]. Although the mechanisms responsible for the pathogenesis of migraine have not yet been fully explained, some of the factors which contribute to its onset have been identified. Specifically, it has been suggested that cortical activation changes are at the base of Cortical Spreading Depression (CSD) which is considered as the pathophysiological basis of the migraine aura [4]. Experimental models examining the role of CSD in migraine have shown an involvement of the trygemino vascular system, whose inflammation is held responsible for migraine pain [5,6].

De Sousa et al. [7] identified the key role played by the dopamine D4 receptor in migraine genesis, too. Moreover, a number of studies have associated migraine clinical picture with metabolic disorders characterized by a genetic Magnesium Deficiency [8,9]. Regardless of what the specific cause is, a common element to all these pathogenic events is found in an altered cortical excitability. In this regard, according to Antal et al. [9], migraine is caused by cortical hyperexcitability [10] due to an abnormal brain response to the environmental stimuli. Indeed, patients suffering from migraine would present a higher amplitude and a lower adjustment to evoked and event-related potentials [11-14] in all sensory domains.

Contrary to what is claimed by Antal, Bohotin et al. [15] argue that the lack of adaptation to environmental stimuli in migraine individuals is due to the hypoactivation of the thalamocortical system. In their rTMS studies the authors showed a reduced cortical mismatch due to a train of excitatory pulses sent to the somatosensory area [16]. A recent theory has proposed a semantic modification able to unify these two opposing hypotheses. The idea is that the cerebral cortex of migraine patients, especially during the inter-ictal period, seems to be hyper-responsive to sensory stimuli rather than being hyper-excitable. Such effect would be demonstrated by the lack of adaptation both to cognitive and sensory stimuli, as reported both in evoked potentials and neuroimaging studies [17].

It would appear that migraine patients show a lower level of sensory cortex pre-activation towards external stimuli, that could be the result of a dysfunction of the thalamocortical system (thalamocortical Dysrhythmia). In the last decade migraine has been studied through non-invasive brain stimulation neurophysiological techniques (evoked potentials, TMS and tDCS) which allowed to better understand its main features [18].

In clinical settings the two most widely used techniques are the repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). The latter is a non-invasive cortical neuromodulation technique which modifies the neuronal firing through the induction of a weak electric current on the scalp of the patient [19]. The stimulation is performed using two electrodes: an anode and a cathode. The modulation induced by the current flow leads to a depolarization of the cortical areas underlying the anode and a hyperpolarization at the cathode site. Specifically, the anodal stimulation would seem to excite the cortical membrane, differently from the cathode which would inhibit it [1,20]. tDCS was successfully applied for the treatment of different neurological disorders [21], thus confirming its ability to modify the dysfunctional neural activation patterns. However, few studies have considered the validity of such a technique in reducing migraine symptoms. Further researches in this direction would have important clinical implications, as they would clarify the usefulness of this method in the treatment of migraine, as well as contribute to validate its effectiveness when combined with pharmacological treatment.

Given these assumptions, the aim of this paper is to provide an overview of the main studies which have used tDCS for clinical purposes in order to examine the potential of this method and outline its possible future developments.

Methods

Literature review

Studies investigating the effectiveness of tDCS in the treatment of chronic headache and migraine were included in this review. The following inclusion and sample criteria were adopted: healthy subjects suffering from headache and migraine; administration of multiple tDCS sessions (no single-stimulation); use of the sole tDCS; no previous administration of tDCS or other brain stimulation techniques. Further inclusion criteria recommended participants being aged between 18-65 and not presenting with previous cerebrovascular or cerebral accidents, neurodegenerative diseases or other concomitant neurological diseases. Similarly, only the studies carried out on subjects without any concomitant psychiatric illnesses or drug addiction were considered in the present review.

Experiments on chronic or episodic headache were included. All the studies on menstrual migraine were ruled out. The following study types were considered: group studies; pilot studies; single cases and metanalysis, reviews.

Search strategy

The studies included in the present review were identified from the following electronic databases: PubMed, Isi Web of Knowledge, Scopus, Psychinfo and Cochraine.

Search terms for studies published between 1985 and 2016 on tDCS efficacy in the treatment of headache and migraine included: "migraine + tDCS" (or transcranial Direct Current Stimulation); "migraine + NIBS (or Non Invasive Brain Stimulation)"; "headache + tDCS (or transcranial Direct Current Stimulation)"; "headache + NIBS (or Non Invasive Brain Stimulation"; "chronic migraine + tDCS"; "episodic migraine + tDCS"; "chronic headache + tDCS"/ "episodic headache + tDCS"; "episodic migraine + noninvasive brain stimulation"/"chronic migraine + noninvasive brain stimulation"/"chronic headache + noninvasive brain stimulation"/"episodic headache + noninvasive brain stimulation"

Results

At first, 27 published articles were identified. Two of the authors of the present paper were assigned to review abstracts/full text of the paper fund in order to include only those which met at least one of the inclusion criteria stated above. Therefore, 22 studies were excluded: 2 studies in the form of abstract for symposia rather than full-articles [22,23]; 9 articles not specifically focused on the therapeutic effectiveness of tDCS in reducing headache/migraine effects, but centred on the abnormal changes of synaptic excitability caused by these disorders [24-32]; 3 papers reporting data both from tMS and tDCS to modulate neural plasticity in migraine and healthy subjects [3,29,33]. Furthermore, 2 studies were ruled out because they specifically focused on menstrual migraine [34,35] and 2 because they did not deal with tDCS in the rehabilitation of these disorders (in particular, Holly-Lee et al. [36] reported non-invasive vagal nerve stimulation, while Uglem et al. [37] discussed about the efficacy of TMS in the treatment of pain in migraine). The study by Martelletti et al. [38] was not included because it just illustrated the position of the European Headache Federation on the use of neuromodulation in the treatment of headache, without specifically describing any example of therapeutic application of these techniques. Finally, the review by Dos Santos et al. [39] was excluded because it just focused on the concept of chronic pain rather than on headache/migraine disorders.

In the light of such analysis, 5 studies were found to meet the inclusion criteria: Viganò et al. [40], Rocha et al. [41], Antal et al. [42], Auvichayapat et al. [43] and Da Silva et al. [44] (Table 1).

Discussion

Finding out the best treatment and prevention for migraine still remains one of the most challenging aspects in in the care of a number of people suffering from this condition, as the drugs currently used in the prophylaxis of this disturbance are unspecific and not always properly effective. Therefore, more disease-specific treatments designed to counteract the dysfunctions involved in migraine pathogenesis are needed. This may be the case of tDCS. The efficacy of this neuromodulation technique in the prevention and treatment of episodic and chronic migraine has been investigated through a review of the main articles on this issue and results are hereby reported. In a first

Table 1. *Summary of study findings.*

First author(s) and year of the study	Purpose	Participant(s)	Design	Expected changes	Study sessions	Tranining	Materials	Stimulation protocol	Results	Neural outcomes
Viganò in 2013	To study the effects of anodal tDCS on visual cortex activity in healthy volunteers (HV) and episodic migraine without aura patients (MoA), and its potentials for migraine prevention.	11 healthy volunteers and 13 migraneurs without aura.	Case control study	To prevent migraine attacks and reduce their duration.	Electrophysiological study (1 session) and therapeutic study (16 sessions).	Two weekly session of stimulation for 8 weeks.	Tdcs, Micro 1401 CED, STATISTICA version 7	Anode was placed over the occipital region near Oz, cathode was fixed on the chin. The subjects were stimulated at 1 mA-intensity flow and each session lasted 15 minutes.	Migraine attack frequency, duration and acute medication intake significantly decreased during the treatment period compared to pre-treatment baseline.	Increased habituation of the VEP N1P1 component. VEP amplitudes were not modified by tDCS
Rocha in 2015	To compare the excitability of visual cortex in migraine patients with healthy volunteers; to modulate cortical excitability in migraine patients with tDCS	Step1: 23 migraneurs and 11 healthy volunteers Step2: 19 migraneurs.	Step 1: cross-sectional study Step2: randomized, double-blinded, controlled pilot trial	To reduce igraine symptoms and to find a correlation between patients' clinical improvements and changes in cortical excitability.	Electrophysiological and therapeutic study	12 sessions (3 times per week) of active (experimental group) or sham (control group) stimulation.	TMS, tDCS	The electrode was positioned over the primary visual cortex (Oz) and the other electrode was placed over the vertex (Cz). The subjects were stimulated at 2 mA stimulation intensity and each session lasted 20 minutes.	Decreased number of migraine attacks, painkiller intake and duration of each attack.	Higher level of cortical excitability in migraineurs compared to healthy volunteers
P. Auvichayapa in 2012	To determine whether 20 consecutive days of left M1 stimulation can be an effective prophylactic treatment for migraine.	42 subjects with Migraine with and without aura	The present study is the first andomized, double-blind, sham-controlled anodal tDCS M1 study on migraine prophylaxis.	To reduce igraine symptoms	1) Pre-treatment baseline evaluation (4-weeks) where attack frequency, pain intensity and dosages of abortive medications were recorded 2) treatment sessions 3) post-treatment observation (12 weeks)	tDCS treatment. Patients were randomized to receive either active tDCS or sham tDCS 1mA, 20 m for 20 consecutive days and follow-up for 12 weeks	tDCS, Visual Scale, Analogue for Pain (VAS)	The anodal electrode was placed at the M1 and the cathodal electrode was placed over the contralateral supraorbital area	The results showed statistically significant reduction in attack frequency and abortive medications at week 4 and 8 after treatment. The pain intensity was statistically significantly reduced at week 4, 8, and 12. All patients tolerated the tDCS well without any serious adverse events	Homeostatic regulation of cortical excitability might occur via corticothalamic loop despite of the different stimulated brain area
A. F. DaSilva in 2012	To investigate the analgesic effects of a 4-week treatment of transcranial direct current stimulation (tDCS) over the primary motor cortex of patients with chronic migraine in a sham-controlled trial.	13 patients with chronic migraine	The study consisted of randomized, single-blinded with external blinded rater, placebo-controlled, proof of principle clinical trial.	- To investigate the analgesic effect of tDSC and to reduce migraine symptoms - to analyse the current flow (electricity field) through brain regions associated with pain perception and modulation.	1)Baseline 2) tDCS treatment 3)Follow-up	10 sessions of active or sham tDCS performed over a 4-week period during weekdays	Neuropsychological evaluation: -Global Assessment (PGA), Clinical Global Impression (CGI), Mini-Mental State Examination (MMSE), Digit Span (forward and backward), High-Resolution Computational Model	Anode electrode (5 cm x 7 cm) was placed over the motor cortex (contralateral to the most or predominant painful side or the side where the symptoms begin) and the cathode electrode (5 cm x 7 cm) was placed over the contralateral supraorbital area	- There was no signficant difference in the general cognitive assessment (MMSE and digit span) comparing the 2 groups who received stimulation. -Mixed ANOVA revealed a signficant interaction effect (between time and condition) for both VAS pain and length of migraine episodes but no signficant changes in level of anxiety	Signficant electric fields were generated, not only in targeted cortical regions but also in the insula, cingulate cortex, thalamus, and brainstem regions.
A. Antal et al. in 2004	To determine whether transcranial direct current stimulation (tDCS) can be an effective prophylactic therapy for migraine and migraine-associated pain.	30 patients (4 drop-out) aged between 18 and 65 years.	Case control study	Reduction in the duration of migraine attacks thanks to the tDCS montage.	1)Compilation of a diary of pain for 8 weeks 2)Treatment Period using tDCS for 3 weeks 3)Treatment period using tDCS sham for 3 weeks 3)Completing of a questionnaire on tDCS	tDCS training. During the first 3 weeks of treatment all patients received only sham stimulation; during the second period, half of them received sham stimulation, while the other half had cathodal stimulation.	tDCS, Questionnaire rating-scale for evaluation	tDCS adopted electrodes (5x7cm). The cathode was placed over the Oz and the anode over the Cz electrode. A constant current of 1mA intensity was applied for 15min.	- Within the cathodal and sham groups, the number of migraine attacks was not significantly reduced - There was a signficant reduction in the duration of migraine-related symptoms after verum stimulation but not in the sham group - There was a signficant reduction in the mean duration of the migraine attacks after verum stimulation but not in the sham group.	A signficant reduction by verum treatment was observed with regard to the duration of migraine and pain intensity

study carried out by Antal et al. [7] the authors tested whether repeated sessions of cathodal tDCS applied over the visual cortex of migraine patients might result in decreased headache frequency, intensity and duration. The choice of inhibiting the cortical excitability of V1 was supported by neuroimaging, electrophysiological and behavioral studies, demonstrating the presence of an abnormal visual cortical processing in people with migraine [9,45-47]. Hence, the authors assumed that inhibitory tDCS over V1 might be effective in migraine prophylaxis by diminishing the maladaptive cortical excitability and, thus, having therapeutic effects. The clinical treatment lasted 6 weeks (3 weeks of sham stimulation and 3 weeks of real stimulation for half of the patients and sham stimulation for the others). Each session included 15 minutes of sham or active tDCS at the intensity of 1 mA, for 3 days/week. The tDCS montage protocol considered the cathode over the Oz and the anode over the Cz electrode positions, according to the 10–20 EEG system. Results revealed a significant reduction of migraine duration and pain intensity, while the frequency of migraine episodes did not significantly diminish. The authors interpreted the latter outcome as a possible consequence of the low intensity of tDCS stimulation. A montage protocol similar to the one described by Antal et al. was also used by Rocha et al. [41]. The authors performed a 2-step trial: firstly, they compared the interictal excitability of the visual cortex in migraine patients with that of healthy subjects. In a second phase, the clinical implications of repeated cathodal tDCS stimulations over the visual cortex were investigated. Results of the first study highlighted the presence of an interictal visual cortical hyperexcitability in migraine patients. As for the clinical study, outcomes related to the number of migraine attacks, duration of each single episode and painkiller intake did not change between the active group and the sham group. The lack of significant difference between groups may simply be due to the small sample of the study. Alternatively, similarly to the findings of a study performed by Antal et al. [7] the intensity or duration of tDCS stimulation could not have been long or strong enough to confirm a clear tendency towards clinical improvement. Further studies are needed to clarify these aspects.

A similar 2-step experimental design aimed at investigating both the experimental and clinical effects of tDCS was performed by Viganò et al. [40]. This study had a twofold purpose, too: in the electrophysiological examination, both healthy volunteers and migraineurs were stimulated in order to ensure that tDCS could modulate cortical habituation and correct the impaired interictal excitability in migraineurs. In this case, contrary to the previous studies, anodal stimulation over the visual cortex was provided. The authors chose to perform anodal tDCS in order to increase visual cortex preactivation and subsequently correct the lack of habituation in migraineurs, with the idea that the habituation deficit typical of these subjects could be the consequence of a lower preactivation level of the brain cortex. Participants were stimulated at 1 mA intensity and each session lasted 15 minutes. In the second study, the same stimulation paradigm was converted into a preventive therapy lasting 8 weeks (2 stimulations/week, for a total of 16 sessions of stimulation). The results of the electrophysiological study are consistent with those found in previous studies using rTMS [45,48,49] where an excitatory 10 Hz stimulation resulted in an increase in the initial lower visual evoked potential response and restoration of normal habituation in migraineurs [19]. However, differently from rTMS, despite an increased cortical habituation in both groups through tDCS, no improvement in the visual evoked potentials initial amplitude was found, neither in healthy subjects nor in migraineurs. The significant increase of habituation in the absence of any initial amplitude modification, i.e. any cortical preactivation level enhancement consequent to tDCS stimulation, is difficult to explain. It could be attributed to the different mechanisms of action of tDCS and TMS. Alternatively, it could be the consequence of inhibitory circuits within the cortex. Still, it might be explained by the fact that impaired habituation does not necessary require a lower preactivation level [50]. As for the therapeutic intervention, results were encouraging: migraine frequency, migraine days, painkillers intake, and attack duration decreased, and this improvement was even stronger in the second part of the treatment. The authors concluded that, even if a single anodal tDCS session over the visual cortex might have short-term effects, repeated stimulations for a longer period could induce neuroplastic changes and sustained modifications within the underlying visual cortex.

The efficacy of tDCS in reducing chronic migraine was also investigated by Da Silva et al. [44]. In their randomised, single-blinded and placebo-controlled study, the authors investigated the effectiveness of an extensive 4-week tDCS treatment for chronic migraine. Contrary to the previous protocols Antal et al. [51], ROcha et al. [52], Viganò et al. [40], where V1 was stimulated, in this study participants were randomized to receive active or sham stimulation over the primary motor cortex. They received a total of 10 sessions over a 4-week period. In active tDCS, the intensity of stimulation reached 2 mA and was applied for 20 minutes. Outcomes of the study demonstrate that tDCS applied over motor cortex can progressively decrease intensity of pain, length of the chronic migraine episodes, and patients' clinical impression.

Also, Auvichayapat et al. [43] investigated in their randomized double-blind controlled study, the efficacy of a repeated anodal stimulation over the left primary motor cortex. The treatment lasted 20 days and included one tDCS/day. The anode was placed over M1, while the cathodal electrode over the contralateral supraorbital area. Intensity stimulation was 2 mA.

Similarly, to the previous study, the authors found that the frequency of attacks in the active group was significantly lower than that measured in the sham group after treatment, even if it did not last for long time, as resulting from follow-up evaluations.

Conclusion

Although the comparison of the results obtained in these studies is limited because of the major differences in their experimental designs, all of them indicated tDCS as a useful clinical tool

in migraine prophylaxis. As reported above, the mechanisms underlying the maintenance of chronic migraine, which might justify the use of non-invasive stimulation protocols, are still controversial. According to a first hypothesis, migraine might be the consequence of primary cortical hyperexcitability [51,53,54]. Thus, habituation impairments in patients with migraine might be due to increasing excitatory mechanisms, probably caused by reduced inhibition resulting from GABAergic system deficiency in occipital cortex [55,56]. Moreover, insufficient glutamatergic function, mutations in the presynaptic calcium, low brain magnesium levels [57] and an abnormal mitochondrial energy metabolism [58-60] may be involved in the maintenance of this complex phenomenon. Alternatively, according to the 'ceiling' theory [61], decreased cortical inhibition [3,22,62,63] or reduced baseline activation of sensory cortices might lead to this condition. These hypotheses are at the basis of a study carried out by Vigano et al. [40], where the authors chose to use anodal stimulation over V1 to enhance the reduced preactivation level of this portion of cortex. A third possible explanation of the maladaptive neural mechanisms underlying migraine is that brain cortex is not hyper excitable itself. Rather, it may be hyper responsive to sensory stimuli in migraine between attacks [27]. Such a hypothesis might explain the results obtained by Rocha et al. in their study [41]. The authors found that the potential positive clinical effects induced by cathodal tDCS were not associated with a reduction of cortical excitability, suggesting that an improvement of clinical measures may occur regardless of the normalization of this excitability. Thus, the efficacy of tDCS stimulation might lay in the reduction of excessive cortical hyperresponsivity between attacks, gradually leading to plastic changes of central structures (DA Silva 2012). tDCS could modulate endogenous pain networks by affecting mu-opioid and glutamate/GABA neurotransmission, resulting in a more functional and/or structural neuroplasticity [44,64]. However, there were significant differences in the neuroanatomical maps of current flow generated by each tDCS montage and in the consequent effect on migraine intensity and frequency. Indeed, while the tDCS montages including cathodal stimulation over the primary visual cortex [41,65] obtained weaker results, significantly more encouraging outcomes were reached following anodal stimulation of the primary motor cortex [43,44]. To this end, it has been suggested that the efficacy of tDCS stimulations on pain relief depends on the projection of fibers from the motor cortex to other structures involved in pain processing, such as the thalamus and brainstem nuclei [31,32,62]. During tDCS stimulation, significant current flow may be induced across the brain, extending from the immediate target cortical regions to the deeper structures. Indeed, while invasive methods include a direct implantation of the electrodes in cortical and/or subcortical structures, in non-invasive approaches the electric field is not restricted to the target region; conversely, it spreads over neighboring cortical and even subcortical regions, according to the configuration or montage applied [66]. Thus, structures which are part of the pain neuromatrix, such as insula, cingulate, thalamus, and brainstem may be functionally activated [44,67,68] analyzed the tDCS-induced electric current flow to the entire cortical surface and deeper brain structures and found that these structures contained significant peaks of electric current in sub-regions related to pain perception and analgesia [31]. In particular, bilateral thalamic activation has been frequently demonstrated in PET and fMRI studies of pain [69-76]; so that its sustained activation during painful stimulation may be a phenomenon predisposing to central sensitization and headache persistence [61]. Also, the insula is involved in pain processing. While the anterior insula is thought to process emotional functions, its posterior part seems to be more related to visceral symptoms, such as pain detection [77]. Thus, the nociceptive input is first processed at the posterior insula, which is likely related to the interpretation of the anatomical location and intensity of the stimulus, and then at the anterior insula, mainly involved in emotional reactions [31,78]. It is plausible that some limitations could have influenced the interpretation of the literature results. Firstly, the limited number of studies might make it difficult to clearly and definitively interpret the data, especially if we consider that most of them used different treatment protocols and electrode montage. A further remarkable limitation of this study is that most of the analysed researches included a small number of participants. In spite of that, as far as we know, this review has been the first to collect the main studies on the efficacy of tDCS in the treatment of migraine, showing that repeated sessions of tDCS may induce more functional and lasting neuroplasticity at the cortico-subcortical level, promoting synaptic and strengthening of the structures targeted, with significant repercussions on the patient's quality of life

Ethical Approval and Consent to Participate

Not applicable

Competing Interests

The Authors declare that there are no competing interests.

Availability of Data and Materials

All the data are available in the following electronic databases: PubMed, Isi Web of Knowledge, Scopus, Psychinfo and Cochraine.

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