Efficacy and mechanisms of transcranial electrical stimulation in headache disorders

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Abstract

Headache is the one of the most common problems contributing to suffering worldwide and sometimes it causes disability. Some patients are unable to use the drugs for various reasons and some are resistant to the pharmacological treatment. Therefore, additional effective non-pharmacological treatments are sought. Transcranial electrical stimulation techniques have been developed as potential therapeutic options. Among these techniques, transcranial direct current stimulation (tDCS) is the only technique studied for the treatment of headache. TDCS is a neurophysiological technique with multifarious advantages encompassing its low-cost, high tolerability and acceptability, comfortable application and the opportunity to use concomitantly with other treatments. Steadily increasing interest in tDCS stems from the multidisciplinary advances in neuroscientific backgrounds of neuropsychiatric diseases. Even though exact mechanisms behind benefits of tDCS have not yet been clearly disclosed, changes in multitudinous chemical and physiological parameters have been demonstrated. The purpose of this review is to summarize what is currently known regarding the effects of tDCS on the treatment of headache focusing mostly on migraine. Herein, tDCS procedures that may be helpful for primary headache treatment were described. TDCS has shown promise for effectively treating primary headaches with no severe adverse effects. The findings indicate that the analgesic effects of tDCS can last for a long period and can occur after the time of stimulation. Additional research is required for the determination of optimized stimulation protocols in each specific headache disorder.

Keywords: Headache, migraine, transcranial direct current stimulation, transcranial electrical stimulation

INTRODUCTION

Headache is one of the most common complaints of the patients in primary health care providers and neurology clinics. The cumulative prevalence of lifelong headache is estimated to be 96% and 40% of patients have tension-type headache (TTH) observed in predominantly women and 16.4% of the general population had migraine with an incidence of 2.38% in Turkey (1, 2). Chronic headaches occur when the primary headaches are not appropriately treated, and if they become chronic, there is a significant burden caused by frequent and severe pain attacks. The worldwide prevalence of chronic daily headache is around 3-5%, most of which is chronic migraine with an incidence of 0.066% in Turkey (2, 3).

The headache classification is based on the International Headache Classification 2018 criteria (4). The most common types of primary headaches are TTH and migraine. Besides, migraine ranks sixth among the diseases that cause disability in the world (5). The cost of labor loss and treatment costs of migraine to the European Union are at an annual level of 10 billion Euros (6). The search for prophylactic effective therapies continues due to the negative impact of migraine on the quality of life as well as the social burden on the family and work life. The most common type of trigeminal autonomic cephalalgias is cluster headache and its prevalence is 0.1% (7). During cluster headaches, very severe function loss occurs due to intensely severe pain and it is also called "suicidal headache" to reflect its impact on the individual.

The main purpose of prophylactic treatment in primary head-aches is to regain normal function for the individual, to reduce the frequency and severity of headache at least for 50%, to prevent the disability and to offer an option without adverse effects, thus reducing the negative impact of headache on the quality of life of the individual. Currently used headache prophylactic treatments either have many undesirable side effects which might cause termination of the treatment or have low effectiveness. Almost all these treatments have actually been licensed for other diseases (e.g., epilepsy, depression, hypertension etc.).

There are some pathophysiological mechanisms supposed to play role in chronic headache such as: 1) central sensitization, defined as an increased sensitivity of the cortical and spinal neurons to the sensory stimulus and malfunction of descending pain pathways (8, 9), 2) an increase in nociceptive A-delta fibre activation may be led to impaired descending pain control which results in increased input to the trigeminal complex (10). Recently, in the pathogenesis of migraine, dysfunction of the somatosensory process against environmental regulators was also suggested (11).

Recent increasing evidence on the pathogenesis of migraine and chronic headaches has led to different perspectives in the development of new therapeutic options for headache prophylaxis, so noninvasive brain stimulation-based therapies have been established for therapeutic purposes, besides other pharmacological treatments. The most commonly studied non-invasive brain stimulation methods are transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS). tES is a general term that defines several techniques depending on the modality of the applied electricity. The modality can be direct current (transcranial direct current stimulation, tDCS), alternating current (transcranial alternating current stimulation), random noise current (transcranial random noise stimulation) and pulsed current (transcranial pulsed current stimulation). Among tES methods, only tDCS was studied as headache treatment, therefore, only the tDCS method will be covered in this article.

The effects reported in tDCS studies are heterogeneous but often promising. It was suggested in several studies that tDCS is a potential treatment option for drug addiction, stroke, drug-resistant epilepsy, Parkinson's disease, chronic pain, Alzheimer's Disease (AD), neuropathic pain, fibromyalgia, depression and migraine (12). When the efficacy of tDCS is sufficiently proven in certain protocols, tDCS seems to have the priority use potential as a first-line therapy in areas with insufficient resources because of low cost, especially in the patients with multidrug use, elderly people, patients with co-morbidity to avoid drug usage such as pregnancy. The purpose of this review is to summarize what is currently known regarding the effects of tDCS on the treatment of headache focusing mostly on migraine.
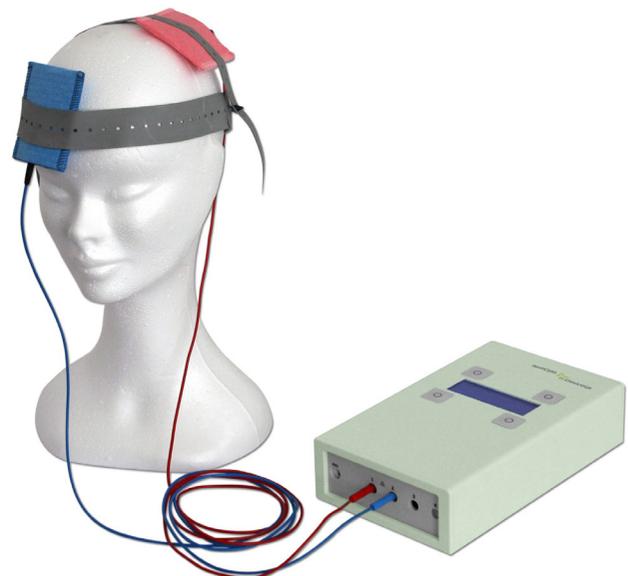
tDCS: An Overview of the Mechanisms and Principles of tDCS

tDCS: Mechanisms of Action

Transcranial direct current stimulation is a neurophysiological technique that modulates the activity of brain regions via applying weak electric currents between two electrodes through the soft tissue and skull (13). In contrast to other forms of brain stimulation, tDCS has numerous distinctive aspects including its low-cost, robust safety and tolerability, low dropout rates, easy application, reliable blinding procedures and the opportunity to use concomitantly with other treatments (14). Thus, tDCS has been the focus of abounding research to understand the neural processes related to cognition, behavior, and pain resulting in the revelation of its potential to induce cognitive, motor and behavioral changes in healthy individuals (15, 16). Ever increasing interest in tDCS resulted in quadruplication of publications in the last five years. Apart from neuroscientific research in healthy samples, the efficacy of tDCS has also been considered to be higher in individuals with disruptions of brain activity. Therefore, tDCS has also become a crucial method in clinical neuroscience, recently. As neuroscientific backgrounds of neuropsychiatric disorders have been disclosed, tDCS has been highlighted as a fruitful intervention in multifarious neurological diseases as well as psychiatric disorders, extending to the recently demonstrated benefits in behavioral addictions (17-19).

Notwithstanding several preclinical experiments and clinical trials have been undertaken to characterize the mechanisms behind the clinical benefits of tDCS, they have not yet been fully elucidated. Although some potential mechanisms have been identified, the overall picture is yet to be far from com-

Figure 1. The demonstration of a typical transcranial Direct Current Stimulation device. Reproduced with permission of neuroCare Group.

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plete. During tDCS, a considerable portion of the electric current penetrates into the cortical tissues to exert the effects of tDCS on neuronal excitability without generating an action potential at the cellular level. Another novel assumption beyond subthreshold stimulation is the redistribution of polarization across the cellular axis to prepare the neuron for easier activation (20). Previous work aiming to decipher the mechanisms of tDCS after-effects has utilized an array of molecular and neuroimaging techniques since changes in neurochemical substrates and functional connectivity of brain areas occur along with the excitability changes elicited by tDCS. Studies co-registering neuroimaging and neurophysiological techniques have implied that anodal tDCS induced an increase of electric activity and regional cortical blood flow (rCBF) during and after the application course whilst cathodal tDCS increased the rCBF during the application and decreased the rCBF after the application (21). These hemodynamic and electrical responses are also seen in remote sites with help of the functional connectivity of the brain networks.

Respecting to the molecular changes, the excitatory peptides such as glutamate, glutamine and neurochemicals associated with neural development and vitality such as brain-derived neurotrophic factor and N-acetylaspartate raise and the inhibitory neurotransmitters like γ-aminobutyric acid (GABA) are diminished (1). Given that GABAergic interneurons play a crucial role in the early stages of AD, tDCS should be kept in mind as a potential disease-modifying treatment in AD. Besides, neuronal excitability changes due to tDCS have been fully blocked by a sodium channel blocker, while a calcium channel blocker, flunarizine only diminished it (20). Changes in acetylcholine, serotonin and dopamine levels may also contribute to the elicitation of the effect (22). D_2 receptors have peculiar importance by virtue of their role in N-methyl-D-aspartate (NMDA) receptor-mediated plasticity (20).

Regarding the short and long-term synaptic plasticity, tDCS has been linked to perpetual shifts of neuronal excitability, similar to long term potentialization and long term depression depending on the stimulus duration and intensity which requires the modulation of the NMDA receptor activity (1, 23). A plethora of research has also indicated that modulating effects have accumulated when using multiple successive sessions which suggests that a consolidation period has been required for exact expression of the beneficial effect. Overall pharmacological, neurophysiological and behavioral studies have confirmed the effects on neuroplasticity yet direct conclusive evidence is still not adequate to draw firm conclusions.

Another mechanism underlying tDCS effects is the modulation of neural oscillations and connectivity as they play a substantial role in diverse neuropsychiatric conditions (1). The modulation also comprises trans-synaptic spreading, determined by the strength and activity level of brain networks. Resting-state functional connectivity changes ensue after the changes of neurotransmitter levels (13). Whilst stimulation over the dorsolateral prefrontal cortex (DLPFC) principally regulates default mode and fronto-parietal networks, stimulation of the motor cortex affects corticostriatal and thalamocortical circuits (13). The polarization effect has also been justified as anodal stimulation generally increases functional connectivity whereas cathodal stimulation has been linked to decreases in functional connectivity (13). In addition, functional connectivity changes during various cognitive and motor tasks have also been shown to be higher than resting-state conditions after tDCS applications (13). To support this notion, online cognitive task performances have been found better than offline administered task performances in a meta-analysis (24). Accompanying functional connectivity changes, tDCS modulates low-frequency oscillations resulting in improvements of cognition and learning (15).

Clearly, the effects of tDCS have been mediated by different indexes of brain activity and the progress regarding this issue is paralleled with the understanding of the neural bases of diagnostic entities. Novel studies should link the treatment outcomes with possible biomarkers of action concomitantly. Future work should also account for brain differences between diagnostic groups and other individual confounders to determine the better optimization of treatment protocols.

tDCS: Principles and Protocols

Adherence to the current guidelines is the vital part of the neuromodulation research to provide proper replicability. Commonly, two conductive electrodes placed in saline-soaked sponges have been attached to head to transfer electric current (13). The most common electrode size is 20-35 cm^2 which provides a current density of ~0.08 miliAmperes (mA) /cm^2. An electrolyte is used to buffer between the electrode and skin. Of note, sponge over-saturation should be prevented to avert the diffuse distribution of electric current to unintended brain regions. Distribution of electric current is also determined by its intensity as well as electrode size and shape. Thus, researchers are strongly advised to report these parameters in the clinical trials. Electrode placement is important for not only targeting the precise locations but also reducing the individual differences. It is broadly derived from the International 10-20 Electroencephalogram (EEG) system, howbeit there are novel and more accurate approaches such as neuronavigational systems or physiological techniques using TMS-EEG as well as high-definition devices providing more focal stimulation (21). Computational models have been utilized to assess the electrical field distribution of tDCS. Proper electrode placement is indispensable for tDCS operators as a 1-centimeter difference in electrode placement results in the distribution of current flow to the unintended targets (21). Finally, the electrode placement is stabilized with the use of elastic straps around the head. Mainly, there is an active electrode and a reference electrode. Cortical excitability around the active (anodal) electrode is upsurged (14).

This result is achieved by increasing the likelihood of action potential generation in the targeted area. This phenomenon has been shown with the help of TMS-EEG methods (14). The reference (cathodal) electrode may be positioned over a target cortical area where inhibition is intended or an extracephalic target. Notably, 2 mA cathodal tDCS may also elicit motor cortical excitability (25). Moreover, the inhibitory effect of cathodal tDCS has been found to be considerably lower than motor cortex stimulation or absent in prefrontal cortex stimulation (26). This may be due to rich and compensatory brain networks associated with cognitive functions controlled by the prefrontal cortex (26).

Device selection is of particular importance as there are only a few certified devices so far (21). Although there is a variety of distinct features such as double-blind mode or availability for other techniques or concomitant usage with neuroimaging methods, basic features of current delivery is common among them (Figure 1).

The motor cortices and prefrontal cortices have been the mostly targeted areas in tDCS applications thus far. Stimulation of the motor cortex is opted in neurological conditions associated with motor dysfunction and pain while flourishing evidence also reveals that stimulation of M1 might modulate cognitive and emotional-affective processes (27). Besides, the stimulation of the prefrontal cortices is usually linked to manifold social, cognitive, affective and behavioral changes.

Blinding is one of the most critical issues in clinical trials. TDCS has a placebo procedure called sham stimulation protocol (21). To apply a sham procedure, stimulation is ramped up and down as in the real condition with low strength and/or durations (< 0.5 mA or < 1 minute). Even though a few studies have reported that sham stimulation might also have elicited some neurobiological effects, it has been proven as a reliable and indistinguishable protocol (28). Blinding integrity of tDCS has been considered acceptable, yet a novel study denoted contradictory results and raised the need for better placebo protocols (15, 21, 29). To this end, different approaches such as crossover applications of opposite montages or active control applications where tDCS is applied to a far target which is clearly unrelated to the assessed parameters should be considered.

Following the line of research since 2000, the mostly opted stimulus duration of tDCS is 13-20-minutes application as it elicits stimulating after-effects up to 90 minutes (21, 30). As a rationale for the sham protocol, a minimum amount of time for tDCS to elicit neurobiological after-effects has been found to be 3 minutes. A duration of 30 minutes may result in the inversion of the stimulation effect (21, 30).

With regard to the moderators of effect, various factors including features of the electrodes, the current intensity, den-sity, duration of stimulation, and the features of the targeted brain areas may moderate or undermine the neurobiological effects of tDCS (15, 22). Although increasing the current density have been claimed to provide better outcomes, it may be associated with tolerability concerns as there is a paucity concerning the safety of current strengths higher than 2 mA as it has only been reported in stroke patients (15). A systematic review and meta-analysis encompassing 61 single-session studies concluded that increment of current density and density charge had resulted in a stronger effect on accuracy without changing reaction times at cognitive tasks in healthy samples (24). Furthermore, this effect was stronger in females. Several reasons including hormonal excitability differences or more trust in top-down control strategies might explain the reported gender difference. Aside from the burgeoning evidence linking increment of intensity to boosted results, the evidence is incomplete and sparse (30, 31). Furthermore, the need for comparative studies including 3 or 4 mA applications still exists.

Apart from the stimulation parameters, there are also individual moderators like age as opposite effects of tDCS on risk-taking have been reported in young and old individuals (8). These distinct physiological and behavioral results might have been possibly linked to differences in GABA related synaptic transmission (32).

The interval between sessions (IBS) is another scantily studied factor which varies from one hour to 2 weeks. A particularly noteworthy study pointed out that daily stimulation has led to more excitability changes than every other day stimulation (33). However, a meta-analysis of single-session studies reported no moderating effect of IBS on cognitive outcomes (34). Of note, the effect of IBS on other outcomes has not been assessed.

Tolerability and Acceptability of tDCS
Safety of a clinical intervention is generally regarded as tissue damage while tolerability refers to all uncomfortable or fortuitous events that possibly affect subject adherence. Concerning safety, evidence derived from animal studies confirm that neuronal damage occurs at current densities of 6.3-13 A/m^2 which is precisely above the preferred densities used in humans ($\leq$ 40 min, $\leq$ 4 mA, $\leq$ 7.2 Coulombs). Accordingly, a comprehensive systematic review including the data of 33200 sessions and 1000 individuals including people with a wide variety of neuropsychiatric conditions reports no serious adverse effects (AE) of tDCS after both single or repeated protocols (35). It was remarkable that none of the convulsive states due to tDCS has been reported thus far. AE rates were also similar among healthy samples and individual samples with neuropsychiatric diseases. Nevertheless, the AE reporting quality is low and a tolerability meta-analysis has not yet been performed. On the other hand, tolerability mainly encompasses mild and moderate AEs. A specific issue here is the elicitation of phosphenes over

the visual cortex which is considerably prevented by ramping the current up and down. Moderate AEs like skin burning have been rarely reported and have been linked to a poor electrode–skin contact. Albeit mild AEs including skin irritation, fatigue and headaches are consistently reported in both active and sham stimulation conditions, they are considered to be transient and low (35). Mild and moderate AEs are strictly related to protocol shortcomings. Thus, a variety of precautions are also applied including the proper electrode placement and skin irrigation with alcohol or scrub to avoid sensation and connectivity reductions. Combined with compliance to standard protocols, usage of certified devices and operator training, tDCS has become one of the most tolerable treatments in neuropsychiatric diseases (21).

A decisive fact to mention is the impact of missing sessions as they are frequently seen but not reported in all studies (36). Loss of efficacy by virtue of missing sessions is still an undetermined issue (36). Yet a ratio of missing sessions below one-fifth of the targeted numbers is generally thought to be acceptable.

Regarding acceptability, a relatively low dropout rate (6-7%) has been reported, chiefly due to AEs and protocol violations (37). Furthermore, about half of the studies report no dropouts. Only 23.4% reported reasons for dropout which are similar between active and sham groups. Future work should report long-term tolerability and acceptability of tDCS applications.

The Clinical Application of tDCS in Anti-Headache Effect
A handful of tDCS studies was published to date in the context of headache treatment and they are very heterogeneous in terms of stimulation parameters, repetition of sessions and indications (prophylactic treatment of various subgroups like episodic migraine, chronic headache, cluster headache, TTH). The intensity of stimulation is usually set at 1 or 2 mA. The polarity of the electrodes is generally anodal. The studied localizations of active electrode placement are primary motor cortex (M1), primary visual cortex (V1), anterior cingulate cortex (Fz) and DLPFC. Each session lasts fifteen to twenty minutes and these sessions was repeated on three to twelve consecutive days or every other day or every day. Sessions repeated once a week or once a month. Most studies focused on migraine because the mechanism is better explained and headache is more severe. The diagnosis, protocols, results of the published tDCS studies in headache are presented in Table 1.

There is only one randomized controlled study using tDCS in the treatment of TTH (38). Hundred patients with TTH were randomized to receive either active or sham stimulation during the headache attack and the pre-treatment and post-treatment pain scores were compared. The results showed statistically significant reduction in pain intensity.

Cortical hyperexcitability plays a role in the pathogenesis of migraine. Since cathodal tDCS suppresses cortical excitability, it can be suggested that this stimulation may be an effective prophylactic treatment in the interictal phase or acute treatment at the attack in migraine patients. So far three studies evaluated the effect of interictal repeated cathodal tDCS application as a prophylactic treatment (39-41). Both three studies examined cathodal stimulation of primary visual cortex (V1) in episodic migraine patients and all studies were designed as randomized controlled. Antal et al applied stimulation for 3 consecutive days for 6 weeks and the results showed only pain intensity reduction (39). Rocha et al. reported reduction in migraine attack frequency, duration and abortive drug usage after 12 sessions of tDCS (41). Lastly in 2015, Wickmann et al. used a protocol in which tDCS was applied 5 days per week, once in a month for 3 months and they revealed a statistically significant migraine attack frequency reduction (40).

In tDCS studies, a significant analgesic effect of anodal M1 and DLPFC stimulation has been demonstrated, therefore, headache studies were performed with anodal stimulation at these locations (42-47). Three randomized controlled studies evaluated the efficacy of anodal M1 tDCS in prophylactic treatment of migraine (43-45). In both studies on episodic migraine patients, the incidence of migraine attacks, pain intensity and abortive medication intake were decreased, and the efficacy duration of treatment seemed to be continued for 3-4 months (43, 45). It has also been reported that treatment has similar efficacy in episodic migraine with- and without aura (45). Da Silva et al. evaluated chronic migraine patients with 10 sessions of every other day stimulation and reported decreased pain intensity and duration, delayed for up to 4 months (44).

Alhassani et al. completed an open label trial in chronic headache patients (3 with chronic migraine, 3 with chronic TTH and 3 with chronic daily headache) to investigate the analgesic effect of 5 consecutive daily sessions of active anodal M1 tDCS plus active spinal cord DCS (tsDCS) (46). The tsDCS anode electrodes were positioned longitudinally over the spinous process of the 10th thoracic vertebrae (T10). With the tDCS and tsDCS treatment, a constant current of 2 mA was applied for 20 min each. They revealed the headache attack frequency reduction in chronic migraine and chronic TTH but not in chronic daily headache, and no change in headache severity and duration in both groups compared to baseline in this small trial.

In 2017, Andrade et al. published a randomized controlled trial to investigate the difference between analgesic effects of M1 and DLPFC in chronic migraine patients (47). The protocol composed of 3 consecutive days per week for 4 weeks of 2 mA anodal/sham tDCS (20 min per day) in 11 patients with chronic migraine. Participants in this study were randomly assigned to one of three treatment conditions: (1) patients with anod-

Table 1. Protocols and results of tdcs studies in headache

Articles	Clinical diagnosis	Study design	Sample size	Anode	Cathode	Stimulation intensity (ma)	Number of sessions (session duration)	Clinical outcomes and results	Adverse effects
Active anodal stimulation									
Solomon et al., 1989	TTH	RCT	100 (50 active, 50 sham)	Active: Left temple	Right temple	0-4 mA	During headache attack (20 min)	Pain intensity reduction	No severe adverse effect. No significant difference between sham and active groups. The most common adverse event was irritation at the electrode sites.
Da Silva et al., 2012	CM	RCT	13 (8 active, 5 sham)	Active: M1 (C3/C4) (contralateral to pain side)	Contralateral SO to active	2	10 (Every other day) (20 min)	Pain intensity and duration reduction. Delayed recovery continued until 4 months.	No severe adverse effect. No significant difference between sham and active groups. The most common adverse event was headache.
Auvichayapat et al., 2012	EM	RCT	37 (20 active, 17 sham)	Active: Left M1 (C3)	Right SO	1	20 Consequent days (20 min)	Migraine attack frequency, pain intensity, and abortive drug intake reduction. Pain intensity reduction at 12 week follow-up	No severe adverse effect.
Vigano et al., 2013	EM	OL	10	Active: V1 (Oz)	Chin	1	16 (2 days per week for 8 weeks) (15 min)	Migraine attack frequency, duration and abortive drug intake reduction. Positive effect takes up to 4 weeks.	No adverse events were reported by patients.
Pinchuk et al., 2013	EM, FETTH, CTTH, CPTH	Retrospective	134 (48 EM, 32 FETTH, 10 CTTH, 44 CPTH)	Active: Fz, Fpz or F2	Ipsilateral mastoid process	0.1	1 day, 5-9 sessions with 4-7 days interval (30-45 min)	In EM and TTH, days with headache, duration and abortive drug intake reduction at Fz localization. Positive effect takes up to 8-10 months.	No adverse events were reported.
Andrade et al., 2017	CM	RCT	11, (4 M1,	Active: Left M1	Right SO	2	12 (3 days per week	Headache impact, pain	No severe adverse effect.

Table 1. Protocols and results of tdcs studies in headache (continued)

Articles	Clinical diagnosis	Study design	Sample size	Anode	Cathode	Stimulation intensity (ma)	Number of sessions (session duration)	Clinical outcomes and results	Adverse effects
			3 DLPFC 4 sham)	(C3) or left DLPFC (F3)			for 4 weeks) (20 min)	intensity reduced: DLFPC>M1	No significant difference between sham and DLFPC groups. M1 group had statistically significant side effects (headache, sleepiness, and itching or tingling on the scalp) compared to DLPFC group.
Alhassani, 2017	CM, CTTH, CDH	OL	9 (3 CM, 3 CTTH, 3 CDH)	Active: left M1 (C3) + T10	Right SO for cranial+ right shoulder for spinal	1	5 consecutive days (40 min=20 min tDCS+20 min tsDCS)	Headache frequency reduction in CTTH and CM. No headache severity or duration change.	No severe adverse effect. Itching tingling, sensation of pins and needles under the electrode was faded away with the session.
Przeklasa et al., 2017	EM	RCT	50 (18 migraine with aura, 12 migraine without aura, 20 control with drug)	Active: Left M1 (C3)	Right SO	2	8-12 (2-3 times per week for 4 weeks) (20 min)	Migraine attack frequency, pain intensity, duration and abortive drug intake reduction in both migraine with- and without aura. Pain intensity and duration reduction continues to 60/120 days after treatment.	No severe adverse effect. 17% tingling sensations under the electrode during the stimulation, 10% fatigue after the stimulation, 3% nausea, 3% headache was reported.
Magis et al., 2018	Chronic Cluster headache	OL	21	Active: Fz	C7	2	Every day for 4 weeks (20 min)	Cluster attack frequency, duration and intensity reduction.	No severe adverse effect. Transient tingling sensation at the electrode site was the adverse event frequently reported.
Active cathodal stimulation									
Antal et al.,	EM	RCT	26	Cz	Active:	1	3 consequent	Migraine attack	No severe

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Table 1. Protocols and results of tdcs studies in headache (continued)

Articles	Clinical diagnosis	Study design	Sample size	Anode	Cathode	Stimulation intensity (ma)	Number of sessions (session duration)	Clinical outcomes and results	Adverse effects
2011			(13 active, 13 sham)		V1 (Oz)		days for 6 weeks (15 min)	duration and intensity reduction.	adverse effect. No significant difference between sham and active groups. Mild tingling sensation, moderate itching, fatigue and headache was reported.
Rocha et al., 2014	EM	RCT	17 (9 active, 8 sham)		Active: V1 (Oz)	1	12 sessions	Migraine attack frequency, duration and abortive drug intake reduction.	No severe adverse effect. No significant difference between sham and active groups.
Wickmann et al., 2015	EM	RCT	16 (8 active, 8 sham)	Cz	Active: V1 (Oz)	2	5 days per week, once in a month for 3 months 15 min)	Migraine attack frequency reduction.	No severe adverse effect. Moderate itching and moderate tingling was reported.

CM: chronic migraine; EM: episodic migraine; TTH: tension type headache; FETTH: frequent episodic tension type headache; CTTH: chronic tension type headache; CPTH: chronic tension type headache; CDH: chronic daily headache; DLPFC: dorsolateral prefrontal cortex; SO: supraorbital; RCT: randomized controlled trial; OL: open label; tDCS: transcranial direct current stimulation; tsDCS: trans-spinal cord direct current stimulation

al stimulation over left M1; (2) patients underwent anodal stimulation over the left DLPFC, and (3) patients in the sham group. They found that headache impact and pain intensity was significantly reduced in only treatment groups, relative to baseline and that anodal tDCS in DLPFC group resulted in significantly greater headache impact and pain intensity reduction than M1 stimulation.

Since, in the previous headache studies, V1 cathodal stimulation was studied, Viganò et al. investigated the effect of anodal V1 tDCS stimulation on headache in an open label study (48). They tested the effectiveness of a total 16 sessions (2 days per week for 8 weeks) days of 1 mA anodal tDCS for 15 minutes over the V1 in 10 episodic migraine patients. They found a significant decrease in comparison to pre-treatment with 4-week follow-up, in migraine attack frequency, duration and abortive drug intake.

There is only one study evaluating tDCS in secondary headache (49). They retrospectively examined the results of 5-9 sessions with 4-7-day intervals of tDCS stimulation on anodal Fz, Fpz and F2 in patients with episodic migraine, frequent episodic TTH, chronic TTH and chronic posttraumatic headache.

In episodic migraine and TTH, they revealed that days with headache, headache duration and abortive drug intake decreased only after Fz tDCS stimulation. There was no change in chronic posttraumatic headache patients and with other localizations.

Last but not least, in an open label study, 21 patients with chronic cluster type headache were applied anodal Fz tDCS as preventive treatment for 20 minutes per day for 4 weeks (50). It was reported that the frequency, duration and severity of the attacks had decreased. In 10 patients, the stimulation was extended to 8 weeks and the frequency of attacks decreased significantly compared to baseline.

No severe adverse event was reported in the studies. The most frequently adverse event was transient discomfort (itching, tingling, sensation of needles) under the electrode.

DISCUSSION

The current evidence of cathodal and anodal tDCS for headache reduction is based on 12 trials investigating clinical primary headache relief. These clinical headache trials applied 1–2 mA anodal tDCS over the M1, V1, Fz or DLPFC or cathod-

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al tDCS over the V1 for 15-20 minutes for different periods. All studies reported positive results 4 weeks after treatment and some of them reported long-term positive activity of up to 3-4 months. No severe adverse effect was found in all of the studies. The only study evaluating tDCS for secondary chronic headache treatment was retrospective and did not produce positive results (49). Overall, tDCS demonstrated a decrease in headache intensity, headache frequency, duration, abortive drug intake and functional impairment in primary headaches. The mechanism underlying the analgesic effect of tDCS is still unclear. In various studies, it has been suggested that tDCS has an analgesic activity by affecting motor, visual, somatosensory, prefrontal function and systems (51, 52).

It is tempting to speculate that tDCS regulates cortical excitability by modulating resting membrane potential and thus altering the spontaneous firing of active neurons (51, 53). In episodic migraine prophylaxis, three randomized controlled trials evaluating repetitive cathodal visual cortex stimulation with different session protocols showed decreased frequency and duration of attacks (39-41). It is not known whether this activity is effective by directly reducing cortical hyperexcitability in the pathophysiology of migraine or by modifying the nociceptive pathways of the spinal trigeminal nucleus in the functional connection between the visual cortex and the brainstem. However, it can be claimed that the inhibition of nociceptive stimuli from the visual cortex to brainstem may reduce pain attacks, according to current data (54).

Studies have shown that anodal M1 tDCS is a useful technique in migraine prophylaxis, but the mechanism of action of anodal tDCS has not been explained yet. Dasilva et al. reported a delayed positive response to anodal M1 tDCS in chronic migraine patients, in addition, other studies in both headache and chronic pain syndromes have supported the analgesic efficacy of anodal M1 stimulation, which is excitatory (42-45, 55). M1 has a connection via a neural network with DLPFC, anterior cingulate cortex, thalamus and cerebellum (56). In the same areas, anatomic and morphological changes were found in migraine patients (57, 58). It has been suggested that M1 is a pain control center in relation to other subcortical areas in some chronic pain conditions, and the analgesic efficacy of anodal stimulation is regulated by electrical flow reaching cortical-subcortical areas associated with pain (44, 59). This assumption is supported by display of electrical fields associated with migraine pathophysiology were generated not only in cortical regions but also in the insula, thalamus, cingulate cortex, and brainstem regions (44). In addition, after M1 stimulation a correlation between pain reduction and a significant increase in the caudal part of the anterior cingulate cortex and a decrease of cerebral flow in the prefrontal cortex was reported (60). These findings demonstrated the effectiveness of motor cortex stimulation with cortical connections as well as subcortical connections.

A randomized controlled clinical study on a small patient group (n=11), which compared anodal M1 and DLPFC stimulation, found that DLPFC stimulation is more effective in migraine prophylaxis than M1 (47). DLPFC is a key locus for emotional regulation and pain control and can provide analgesia by modulating cerebellar areas where it is associated with a neural network (61, 62). In addition to its functional connectivity with M1, DLPFC also has connections to multiple cortical and subcortical areas such as premotor cortex, supplementary motor area, cerebellum and basal ganglia (63). A functional MRI study supplied evidence that the DLPFC-tDCS modulated activity in the caudate nucleus and anterior cingulate cortex as well (64). These findings support that tDCS can induce changes not only in the stimulation area but also in more remote and deeper areas. In addition to the analgesic effect of DLPFC, positive effects on working memory, cognitive function and depression were also shown (12). Therefore, it can be argued that it regulates pain through emotional-cognitive networks. However, it was found that anodal DLPFC tDCS had analgesic activity independent of mood, fatigue, or attention changes (65).

A single study demonstrated that anodal stimulation of the visual cortex in migraine prophylaxis is also effective (48). Recently, it has been suggested that hyper-responsiveness to sensory stimuli may be responsible for migraine pathogenesis instead of the hyperexcitability (66). This hypothesis was further supported by evoked potentials and neuroimaging trials in which hyperresponsiveness emerged as a result of lack of habituation to sensory stimuli (67). Topiramate, the most effective drug used in migraine prophylaxis, has been also shown to normalize this well-demonstrated habituation (68). This mechanism may explain how the anodal stimulation is also effective in the region where cathodal V1 stimulation is effective.

While there are many centers in brain known to be associated with pain control, these centers could not show superiorities in the pain studies because they showed moderate to high effect size in the decrease of pain and reduction of pain killer drugs intake (69). Latin America consensus recommends anodal M1 tDCS with level B evidence for migraine prophylaxis but a single study suggested that DLPFC had better effects for headaches (47, 70). Therefore, further well-designed clinical studies are needed to determine which protocol would be more effective in primary headache patients.

CONCLUSION

In primary headaches, tDCS is promising as a nonpharmacological prophylactic treatment option without severe adverse effects especially for patients who could not receive pharmacological treatment and those who are drug resistant. In headache studies, most frequently stimulated areas with tDCS were cathodal V1 and anodal M1. The speculated mechanisms of action were that the cathodal V1 stimulation inhibits the hyperex-

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citable visual cortex, while the anodal M1 excites primary motor cortex to reduce the pain perception. Repetitive application of stimuli is necessary to ensure modulation. Currently, there is no certain well-established tDCS protocol for the treatment of headache. Well-designed large-scale studies of tDCS stimulation, which include different severity, frequency, and electrode localizations, will enable detection of optimized stimulation protocols for relieve the substantial burden of headache.

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