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Effectiveness of cathodal tDCS of the primary motor or sensory cortex in migraine: A randomized controlled trial

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ABSTRACT

Objectives: Transcranial Direct Current Stimulation (tDCS) is a new technology that is extensively used for migraine treatment. The present study aims to examine the effectiveness of cathodal-tDCS (c-tDCS) in decreasing migraine pain frequency, duration, and intensity at the right primary motor cortex (M_1) or sensory cortex (S_1) in individuals with episodic or chronic migraine.

Methods: The present study has a randomized, single-blind, and sham-controlled design. It tests the effectiveness of 22 sessions of c-tDCS (20min/1000 μA) in 45 migraine patients (episodic = 35; chronic = 10/with aura = 28; without aura = 17). Spread over 10 consecutive weeks, the sessions started with three sessions per week and ended with one session per week. Participants were tested at the baseline, at the end of intervention, and at 12-month follow-up. The migraine diagnosis was based on criteria set by International Headache Society (IHS) and patients were allocated to two experimental ($n_{m1} = 15$; $n_{s1} = 15$) and a sham intervention group ($n_c = 15$).

Results: The results of a series of MANCOVAs showed a significant reduction ($p < 0.05$) in all hypothesized symptoms of migraine pain in both experimental groups compared to the sham intervention group at the posttest and follow-up.

Conclusion: The application of c-tDCS to M_1 or S_1 can be used as a technological intervention for the prophylactic and therapeutic treatment of episodic or chronic migraine.

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Introduction

Migraine is a cumbersome, multifactorial, and circuit-related disease that causes obvious alterations in various cortical networks [1–5]. The repetitive presence of excitatory or inhibitory response-related activities in these networks are notable instances of such alterations in a migraine brain [6]. *Contextually*, pain processing is related to the somatosensory cortex so that abnormal inhibition is observed in the motor cortex of migraine patients [7–10]. Furthermore, motor cortex projects bilateral and ventral connections almost in all brain areas [11]. *Functionally*, these connections form various cortical-dependent network dynamics as well as modulatory and corticocortical feedback signaling circuits in the brain [12]. For example, the amplification of rhythmic cortical feedback during thalamocortical oscillations in a migraine brain represents a form of corticocortical feedback signaling [13]. Allostatic loop system and network system oscillations influence dendritic or amplitude modulation (AM) and axonal or frequency modulation (FM) systems [14]. The excitatory alterations in these systems influence the reciprocal connectivity between receptor-synaptic potentials and action potentials [14,15]. Accordingly, informed by sensory-motor-network interactions and stress response domain interplayers, the electrophysiological homeostasis is altered abnormally (allostatic load) in a migraine brain [16,17]. Therefore, there are context-dependent and functional rationales to propose a new technique for modulating a migraine brain in the present study.

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Moreover, evidence suggests atypical sensory processing in the cortex of migraine patients, especially in the somatosensory, visual, and olfactory-related areas [18,19]. The results of a study based on whole-head magnetoencephalography (MEG) showed aberrant functional connectivity between the sensory cortex and the frontal cortex in a group of migraine patients compared to a healthy control group [20]. A similar study with MEG and finger-tapping task indicated motor cortex hyperactivity in a group of migraine patients [21]. The results of a meta-analysis demonstrated the role of motor cortex maladaptive plasticity and abnormal inhibition in patients with chronic pain [22]. Consequently, these variabilities complicate the treatment of migraine. Pharmacological, psychological, and invasive interventions have been employed for migraine treatment. Each of these interventions has certain therapeutic shortcomings or undesirable side effects, e.g., Botulinum toxin [23–27]. Tolerance, tachyphylaxis (due to Na, K-ATPase-related alterations), drug dependence, and drug-induced toxicity either to over-the-counter drugs, sedatives, selective serotonin reuptake inhibitors (SSRIs), or migraine-specific medications are the undesirable side effects, which restrict the use of medication-based interventions [28–31]. Besides, medication is likely to transform episodic migraine into chronic migraine [30]. The transformation is largely due to the repetitive presence of maladaptive excitatory, inhibitory response-related activities or electrophysiological dysresponsiveness in a migraine brain [32–34].

To overcome the current shortcomings associated with the treatment of migraine, a new, safe, well-tolerated, convenient, multifunctional, and non-invasive form of intervention known as transcranial Direct Current Stimulation (tDCS) has been introduced [35–37]. There is ample evidence that it boosts the effectiveness of tDCS due to its contextual and functional relevance to migraine. This technology is a neuromodulator that could be used with a cumulative cascade design in migraine brains characterized by cumulative feedforward or allostatic cascade response [16,38,39]. Nonetheless, tDCS can be applied to the target areas on the brain using two modes of polarities. The more popular mode of application is anodal (a-tDCS). In the literature, this mode is recognized for its excitatory effect whereas the cathodal mode (c-tDCS) is almost known for its facilitative effect on the brain [40,41]. Given the hyperactive status of a migraine brain and the following reasons, c-tDCS is expected to offer several advantages over the more customary anodal mode. *First*, a migraine brain has a lower cortical threshold for cortical spreading depression (CSD) [42,43]; therefore, amplified CSD propagation velocity using a-tDCS can potentially *increases* the probability of migraine attacks [44]. *Second*, a migraine brain is characterized with a lower sensory and pain threshold [45]; thus, a-tDCS can potentially *lower* the sensory and pain thresholds and raise the probability of migraine attacks [46]. In contrast, it has been shown that the application of c-tDCS to M_1, S_1, somatosensory, or dorsolateral prefrontal (DLPFC) cortices diminishes pain perception and increases sensory and pain thresholds [46,47]. *Third*, the role of calcitonin gene-related peptide (CGRP) in a migraine brain is clear and the activation of this gene receptor on Aδ-fiber leads to the sensation of pain [48]. Congruently, applying c-tDCS to S_1 decreases the pain threshold [49,50]. *Fourth*, S_1 and M_1 are identified as a part of pain-related neuromatrix, and therefore applying c-tDCS to S_1 or M_1 can reduce brain hyperexcitability and lower sensory and pain thresholds [51]. However, evidence on the relative effectiveness of previous tDCS protocols is scant and inconclusive, largely due to methodological limitations such as sample size, session design, randomization, lack of a control group, and insufficiency or absence of follow-up [38,52,53]. Informed by the above debate and previous observations [54–56], we hypothesized that applying c-tDCS to the right M_1 or S_1 can lessen pain intensity, duration, and frequency in a migraine brain.

Table 1
Mean and standard deviation for demographic information and history of migraine in study groups.

	Group		
	M_1; Mean (*SD*)	S_1; Mean (*SD*)	Sham; Mean (*SD*)
Age	36.40 (13.18)	34.06 (11.51)	33.66 (11.28)
Weight	59.40 (6.99)	61.40 (17.86)	63.66 (9.17)
Height	163.26 (6.27)	161.80 (8.40)	159.00 (7.47)
History of migraine	13.66 (11.97)	9.46 (5.16)	10.23 (8.54)

Note. M_1 = Motor Experimental; S_1 = Sensory Experimental.

Methods

Participants

The final sample size consisted of 45 participants (mean of age = 35.49; *SD* = 12.02; range, 18–57) selected from among 432 individuals with migraine who met the study exclusion and inclusion criteria (see below) and consented to the terms of the study. The participants that remained in the study were Persian-speaking residents of Mashhad with a female-male ratio of 1: 0.125 (or 40 females and 5 males). The median of gross family income in the sample was $5,250.00 (range of 2,000.00–9,000.00) per year (2016). Sixty percent of participants in the sample were employed (full time = 44.4%; part time = 55.6%). All participants were living either with their husbands (88.2%) or with their wives (11.1%) except for three single young women (6.6%). 88.2% of women and all men in the sample had children. All participants were right-handed (Edinburg Handedness Inventory [57]). The participation was on a voluntary basis and lasted from June 2015 until February 2018 (follow-up). Table 1 shows mean and standard deviations for demographic information and history of migraine for each study group.

Participants were recruited from a local state hospital. Exclusion criteria were (a) a history of any other neurological disorders; (b) experience of any kind of brain stimulation; (c) metal implants in the upper limb including head and neck; (d) use of any type of medication including over-the-counter pain medicines; (e) concomitants diagnosis of headache disorders, especially medication overuse headache, and (f) use of any other migraine treatments. The use of concomitant medication was prohibited during the tDCS intervention period and at least three months in advance of the intervention [58]; however, there was no prohibition to use pain medications between posttest to follow-up assessment. Inclusion criteria were (a) 18–60 years of age; (b) a confirmed diagnosis of migraine based on the International Classification of Headache Disorders III beta edition (ICHD-3 beta) [59], and (c) a history of migraine in the last 12 months regardless of the disorder type, i.e., without aura (MwoA) or with aura (MwA). Table 2 shows the distribution of participants based on gender, education level, and migraine type for each study group.

Two consultant neurologists at the hospital interviewed and confirmed the migraine diagnosis based on the IHS criteria [59]. Changes of symptoms and signs in female migraine patients (migraine pain frequency, duration, and intensity) were recorded before, during, and after menstrual cycle. Since there were not any changes in the pattern of patients' attacks during their menstrual cycle, further assessments deemed unnecessary. All participants were informed about the goals of the study prior to the intervention. They were informed that their participation was voluntary, and they could abandon the study at will. The rationale behind the

Table 2
Distribution of participants based on gender, education level, and type of migraine in study groups.

Variables		Group		
		M_1; N (%)	S_1; N (%)	Control; N (%)
Gender	Female	12 (26.66%)	14 (31.11%)	14 (31.11%)
	Male	3 (6.66%)	1 (2.22%)	1 (2.22%)
Education	No Education	4 (8.88%)	4 (8.88%)	2 (4.44)
	School education	3 (6.66%)	5 (11.11%)	6 (13.33)
	Higher education	8 (17.77%)	6 (13.33%)	7(15.55%)
Migraine	Acute	11 (24.50%)	12 (26.66%)	12 (26.66%)
	Chronic	4 (8.88%)	3 (6.66%)	3 (6.66%)
	MwA	10 (22.22%)	7 (15.55%)	11 (24.44%)
	MwoA	5 (11.11%)	8 (17.77%)	4 (8.88%)

Note. M_1 = Motor Experimental; S_1 = Sensory Experimental; MwA = Migraine with aura; MwoA = Migraine without aura.

contraindication of pain-related medications including over-the-counter drugs during the present study was also explained to participants. The intake of such medications may adversely influence the effectiveness of tDCS intervention [58]. The Ethics Committee of Mashhad University of Medical Sciences approved the study. Written informed consents were also obtained from the participants. Participants in the sham intervention group received c-tDCS after the follow-up assessment.

Experimental design

A 3 × 3 factorial design (three groups and three dependent variables) was used to examine the effectiveness of c-tDCS in frequency, duration, and intensity of migraine pain in two experimental groups and a sham intervention group. It was a single blind study, meaning that only participants were blind to the nature of procedure. In other words, the experimenter was aware of the experimental or sham groups to which participants were assigned.

Participants who met the study criteria for either MwA or MwoA (whether episodic or chronic) were selected and tested over a 30-week period. They were screened for intensity, duration, and frequency of attacks in the last consecutive three months, as verified by the ICHD-3 beta edition [59]. Participants were randomly assigned to one of c-tDCS experimental groups (M_1 (n = 15) and S_1 (n = 15)) or sham intervention group (n = 15). To ensure comfort and relaxation of participants, they were asked to discuss the feelings they had after the electrical current was switched off. A research assistant, who was not blind to the procedure, numbered and analyzed all the records. However, one of the co-authors who was blind to the group allocations oversaw data analysis. Each participant remained in the study for 10 weeks. All participants received 20 min of 1000 μA stimulation. Evidence does not suggest any difference between moderate (1000 μA) and intense (2000 μA) current modulations applied by tDCS hence due to hypersensitivity/hyperresponsiveness of a migraine brain [60,61] we applied a moderate current in the present study. They received three sessions of c-tDCS per week for five consecutive weeks (on even days, Saturdays, Mondays, and Wednesdays) and then two sessions per week for a two-week period (on Saturdays and Wednesdays), followed by one weekly session over the last three weeks (on Mondays). Friday is a weekend in the region where the present study was conducted.

To measure pain duration, frequency, and intensity, migraine and headache measures (see below) were administered at the baseline, at the end of intervention, and at12-month follow-up. Moreover, telephone contacts were made at three-month intervals to enquire about the participants' experiences of pain or any other undesirable side effects. The main rationale behind these telephone contacts was to minimize participants' dropouts. Besides, the participants were told that they could have control visits along this period if they experienced any migraine attacks or complications that might demand resuming their usual medication. However, none of participants in the experimental group reported referring to their medical doctor or resuming the consumption of migraine medication at any of the telephone contacts or follow-up assessments hence these data were not subjected to statistical analyses. The follow-up examiner was the same experimenter who administered measures at the pretest and posttest assessments. Fig. 1 shows the study flow.

Direct Current Stimulation procedure

A pair of wired carbon electrodes (cathodal size = 3 × 5 (15 cm^2); anodal size = 5 × 7 (35 cm^2)), covered by sponges (soaked in 0.9% saline) was used to transfer electricity from a battery-driven current stimulator (Neurostim 2 Brain Stimulation Device™; MedinaTeb Co.). A smaller carbon cathodal electrode was applied to enhance the specificity of the current stimulation and a larger anodal electrode was employed to minimize any potential discomforts (e.g., pain or tingling) normally associated with the flow of current during anodal stimulation. The device used in the present study has a smart scan monitoring system that provides live digital information about the connection and direct current. The active electrode (cathode) was placed on C_4 in the M_1 experimental group [46,62–64]. In S_1 experimental group, the cathode was mounted on the same side, between C_4 and CP_4 but closer to CP_4 (see Fig. 2) [65]. Fig. 2 shows electrode placement for S_1 experimental group.

Considering the hyperresponsiveness of a migraine brain and the cortical excitability induced by a-tDCS [66–69], the reference electrode (anode) was placed extracranially on the upper part of the left arm. A direct current with an intensity of 1000 μA [61,70] was applied for 20 min every session during the study period [71]. As for the sham intervention group, the electrode was placed on M_1 for the same number of sessions. The sham intervention procedure resembled that of the experimental groups. However, the sham key on the device was switched on for the sham intervention group. In this mode, the device delivers the electrical current only for the first and last 30 s of the experiment, which might provoke a tingling, itching, or burning sensation in the participant to simulate normal stimulation throughout the session. None of the groups received any other treatments or therapies (neither prophylactically nor therapeutically) even if they had migraine attacks during the intervention procedure [58]. All participants had the contact number of the experimenter (highly trained in pain management) in case they needed to share their feelings of pain or had any questions regarding different aspects of the study. Due to the measures taken during the study to maximize participation, no drop-out was observed.

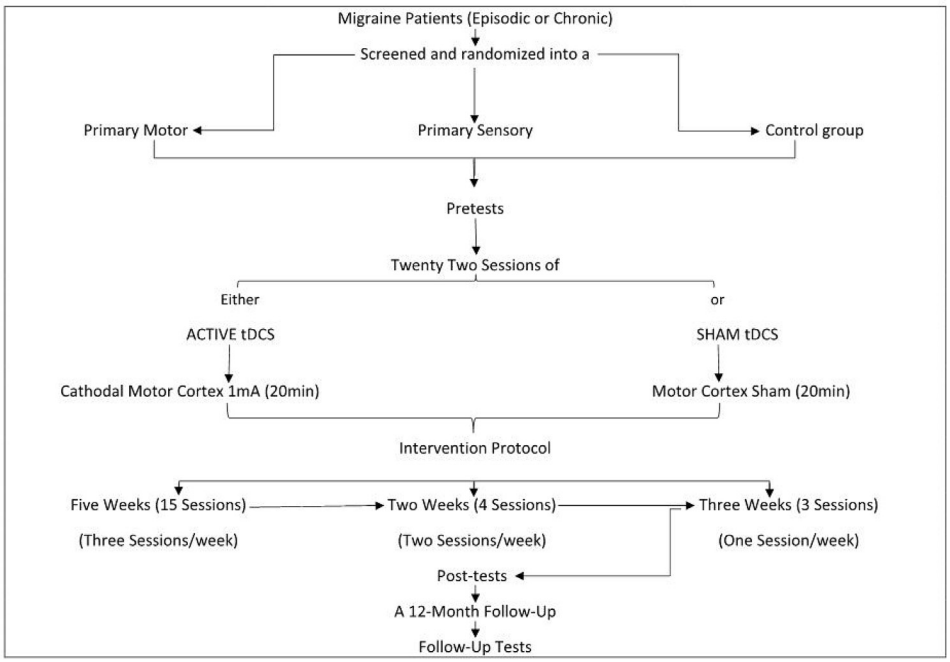

Fig. 1. Flow of the study (screening; from June 2015 to February 2018) and the study protocol/design.

Procedure

The intervention was conducted in a room with controlled noise and lighting. The participants sat at a comfortable resting chair equipped with an adjustable headrest during tDCS administration. To respect cultural norms, a female experimenter was instructed to administer tDCS protocol for female participants.

Measures

Migraine screening measures

An initial screening of migraine was conducted using the Migraine Screen Questionnaire (MS-Q) at medical centers by specialists [72]. This screening tool was developed to measure headache-related complications. The authors reported acceptable reliability and validity scores of this measure [72]. However, to ensure that all participants meet the study inclusion criteria for migraine, a more comprehensive evaluation was conducted using the ICHD-3 beta edition [59].

Headache diary

The Headache Diary [73], which records the frequency (one attack per month, one attack in two weeks, two or three attacks per week, or more than three attacks per week), duration (4, 4–24, or 24–72 h per attack), and intensity (1–3 = moderate, 4–7 = severe, and 8–10 = worse possible case) of migraine attacks over the last thirty days was used to measure the effectiveness of c-tDCS before and after the intervention, and at a 12-month follow-up [73]. The authors reported that the reliability and validity of this measure was desirable [73].

Data analyses

Initially, data evaluation was performed for M_1, S_1 experimental and sham-intervention groups to ensure that there was no missing data. Then, homogeneity, linearity, and normality of variance-covariance matrices were assessed. A p-value ≥ 0.05 was set for all analyses.

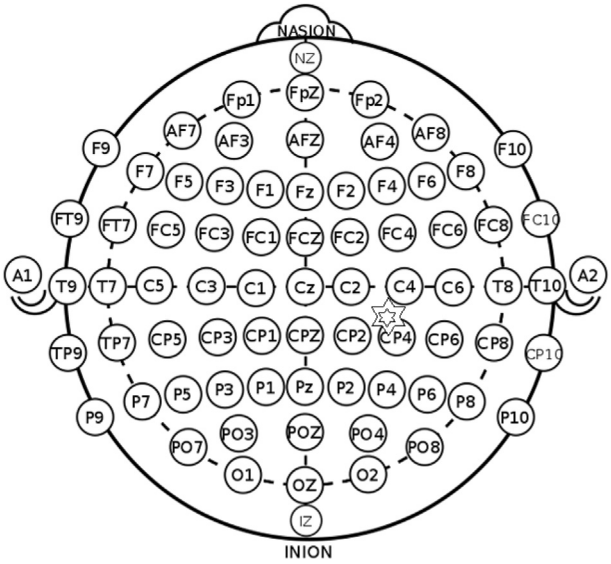

Fig. 2. Electrode placement for S_1 experimental group is marked by a star between C_4 and CP_4.

Results

Table 3 shows means and SDs for frequency, duration, and intensity of migraine pain in each study group at pretest, posttest, and 12-month follow-up.

To examine the relative effect of cathodal stimulation on migraine pain characteristics, three multivariate analyses of covariance (MANCOVA) were conducted. In each model, groups (i.e., M_1, S_1, and sham-intervention) were entered as factors, and age, BMI, history of migraine, education level, and pain characteristics at pretest were entered as covariates. In turn, frequency, duration, and intensity of pain at posttest and follow-up were entered as dependent variables separately in all three MANCOVA

Table 3
Mean and SDs for frequency, duration, and intensity of migraine pain in each study group across three assessment points.

Groups		Frequency			Duration			Intensity		
		Pretest	posttest	Follow-up	Pretest	posttest	Follow-up	Pretest	posttest	Follow-up
M1	Mean	17.13	1.80	2.93	9.87	.87	2.20	7.67	1.40	2.00
	SD	10.049	1.082	1.53	7.40	.35	1.26	1.71	.910	1.36
S1	Mean	14.00	1.67	2.20	9.80	.80	1.93	6.47	.93	1.27
	SD	8.61	1.17	1.93	7.975	.41	1.387	1.64	.704	.704
Sham	Mean	13.13	10.27	10.93	9.47	9.40	10.87	7.60	7.00	7.13
	SD	9.13	7.73	7.076	8.052	7.92	12.46	2.13	1.89	1.85

models. The results of models' fitness test did not reveal a violation of underlying assumptions. In each model, there was a significant multivariate main effect for c-tDCS (M_1-S_1) on all migraine pain characteristics at posttest and 12-month follow-up. Pairwise comparisons indicated significant improvements in all migraine pain characteristics in both experimental groups at the posttest and follow-up (see Table 4). The comparisons did not show any significant differences between the two experimental groups (i.e., M_1/S_1). The effect sizes of all models were greater than Cohen's d = 0.80 for a large effect size.

The only constant irritant in almost half of participants was a sense of mild tingling in the first 20 s (not ramp-up) and final 45 s of the main stimulation. With regard to c-tDCS intervention side effects, 17.77% of M_1 experimental group, 8.88% of S_1 experimental group, and 20% of the sham intervention group reported tingling, itching, or burning sensations during the intervention; however, the sensations were mild, and none of the participant complained of any irritating negative feelings. In addition, the results of a follow-up an hour after each tDCS intervention manifested that only 6.66% of M_1 experimental group, 8.88% of S_1 experimental group, and none of the sham intervention group reported a mild, short-lived headache, which was different from their migraine pain.

Discussion

The present study aimed to examine the effectiveness of cathodal-transcranial Direct Current Stimulation (c-tDCS) in the right primary motor cortex (M_1) or sensory cortex (S_1) in migraine patients. The results exhibited the significant effect of both c-tDCS M_1 and S_1 protocols on reducing migraine pain frequency, duration, and intensity (Table 4). By making changes in cascades of mechanisms, including activation [74], modulation [75], and modification [76], tDCS can improve brain pain-related plasticity [77]. Modification in the pain-related plasticity of brain may be related to altered connectivity, habituation, or altered sensitization. Other studies [78,79] have reported modified habituation in the pathophysiology of migraine. Besides, the effect of tDCS on characteristics of migraine could be due to the modified cortical spreading depression (CSD) [80]. The latter plays a key role in abnormal ion homeostasis or migraine pathophysiology [81].

Primary motor cortex was selected as the site of stimulation as it is a major component of pain matrix consisting of three mechanisms: (a) bilateral: putamen, thalamus, insula, anterior cingulate, and secondary somatosensory cortex; (b) contralateral: primary somatosensory cortex and supplementary motor cortex, and (c) ipsilateral: ventral premotor area [82,83]. Through layer V or pyramidal neurons, the M_1 establishes several caudal and rostral connections with somatosensory cortices and other brain structures including thalamus medial dorsal nucleus, hypothalamus, and periaqueductal grey matter [84], each of which playing a specific role in the pain processes. From a functional perspective, M_1 modulation might lead to pyramidal or extrapyramidal modulation (i.e., excitation or inhibition) in many other structures [85]. Moreover, the right hemispheric lateralization of pain processing [54] is another rationale for choosing this side of cortex as the site of modulation. Thus, the modulation of S_1 was selected due to its reciprocal connectivity to other cortical and subcortical areas, especially M_1 [86]. The primary sensory cortex is a part of the multisensory integration system [87,88]; therefore, the stimulation of S_1 can reduce synaptic deficit or lock [89,90] during subsequent multisensory integration in a migraine brain [91]. Although there is a consensus over the inhibitory effects of c-tDCS on brain activity, several studies [71,92] have revealed that with the extension of c-tDCS beyond 12 min, the current effect shifts to a facilitative state. This actually reduces synaptic lock, whereas a current stimulation based on excitatory mode will lead to higher synaptic hyperexcitability or dysresponsiveness in a migraine brain [68,69,93]. In the same vein, evidence suggests that migraine patients have a lower threshold (elevated sensitivity [44]) in terms of CSD [42,94].

Table 4
Results of three MANCOVA models testing inter-group effects at posttest and a 12-month follow-up.

DVs		Assessment	Main Effects				Covariates: p (η^2)					Pairwise comparisons ($p < 001$)
			Wilks' λ [4,72]	F [2,45]	p	$\eta 2$ (Cohen's d)	Age	BMI	Yrs.	Edu	Pretest	
Migraine attacks	Frequency	Posttest	14.25	30.14	.001	.62 (2.55)	.63 (.001)	.81 (.001)	.46 (.01)	.52 (.01)	.001 (.407)	M_1&S_1 < Ctrl
		Follow-up		39.98	.001	.68 (2.94)	.21 (.04)	.93 (.46)	.75 (.001)	.60 (.001)	.001 (.525)	M_1&S_1 < Ctrl
	Duration	Posttest	11.45	30.96	.001	.63 (2.60)	.84 (.001)	.06 (.08)	.23 (.03)	.32 (.02)	.001 (.411)	M_1&S_1 < Ctrl
		Follow-up		15.83	.001	.46 (1.85)	.77 (.001)	.15 (.05)	.39 (.01)	.16 (.05)	.001 (.446)	M_1&S_1 < Ctrl
	Intensity	Posttest	34.10	125.10	.001	.87 (5.17)	.17 (.05)	.77 (.001)	.53 (.01)	.51 (.01)	.001 (.347)	M_1&S_1 < Ctrl
		Follow-up		91.97	.001	.83 (4.41)	.42 (.01)	.65 (.001)	.73 (001)	.90 (.001)	.001 (.378)	M_1&S_1 < Ctrl

Note. DVs = Dependent Variables; Yrs. = History of migraine for each study group; η^2 = Eta-squared; Cohen's d 0.20 = small; 0.50 = medium; and 0.80 = large effect size.

Nevertheless, it is also postulated that applying c-tDCS to S_1 modulates thin myelinated Aδ-fibers and enhances the brain sensitivity threshold [50]. Additionally, if migraine is assumed to be related to a maladaptive habituation in the brain, administering c-tDCS to M_1 or S_1 is preferred as it facilitates the habituation [53].

In the present study, a novel mode was used for the application of c-tDCS protocol (see Fig. 1) to minimize constant current sensitivity [95]. Thus, to decrease the probability of cumulative cortical sensitivity [60], sessions were held every other day. It should be noted that a daily application of tDCS runs the risk of activating proinflammatory interactions via positive feedback loops including the axis between Cyclooxygenase (COX), Calcitonin Gene-Related Peptide (CGRP), cytokines (e.g., IL-1β), or other innate immune interaction responses in a migraine brain [96,97]. The reference electrode (anodal arm) extracephalic positioning and the larger type of this electrode were among the innovations utilized in the present study (i.e., cathodal = 3 × 5 (15 cm^2) and anodal = 5 × 7 (35 cm^2)). According to the literature, a migraine brain is characterized with hypersensitivity or hyperresponsiveness [66,67] and a-tDCS causes cortical excitability [68,69]. Therefore, it is counterintuitive to apply both electrodes to the skull, and the extracephalic application of reference electrode was the correct strategy to deal with this contradiction. Moreover, according to the literature [98], extracephalic montage improves the density of current in the primary motor and sensory cortices, without a significant modulation in the activities of the brainstem and cervical spine [99]. A distinctive feature of the present study was its 12-month follow-up, which exhibited the sustainability of c-tDCS outcomes for migraine patients even in the absence of booster sessions.

We found only one study [100] with a relatively similar method that had an eight-week follow-up. The authors reported significant improvement in migraine patients. The c-tDCS protocol that they applied to the visual cortex had positive effect on the duration and intensity of each attack, but not for its frequency. This could be due to differences in the polarity of electrodes and the study design. Another study [101] evaluated the effect of applying c-tDCS to visual cortex in migraine patients. The authors reported positive outcomes of c-tDCS application to the visual cortex in terms of frequency and duration (but not intensity) of the migraine pain. The current applied was intense enough (2000μA/20 min) to sensitize a migraine brain (resistance). There was, nonetheless, one reservation relating to the polarity of electrodes (Oz-Cz) [56]. When electrodes are positioned adjacent to each other, the current flows through the surface of skull. Further, they did not run a follow-up assessment. Another study [102] also reported similar posttest effects following the application of c-tDCS to the supraorbital area. They, however, did not control participants' use of medications, which was one of the exclusion criteria in the present study. The c-tDCS application to M_1 or S_1 (intracranial) generates positive outcomes that endured for 12 months in the present study.

However, participants of the present study were not homogeneous in terms of gender and migraine type. Therefore, it is recommended to study various groups of migraine patients based on their gender and migraine type. Further, given that the present study was undertaken within an Eastern culture, future studies could replicate this study for migraine patients with various cultures and ethnical backgrounds. In addition, since the research assistants administering the c-tDCS technique for all participants had to switch on or off the sham button on the device and put electrodes on the scalp, they could not be blind to the participants' allocation. Since the tDCS used in the present study could not be programmed for automatic, randomized allocation of participants into the study groups was not possible to meet standards of a double-blind design. To adopt a double-blind design in the present study, we needed to employ two experimenters for each gender group (due to cultural considerations), which could introduce another source of bias to data collection. Another potential limitation of the present study could be the distinction we drew between M_1 and S_1, whereas these areas could be claimed to be interconnected, short-distanced, and overlapping. At least, applying c-tDCS to M_1 or S_1 reveals that stimulating either of these areas can reduce migraine pain despite their potential overlapping states. Moreover, the following methodological alternatives can be addressed in future studies: (a) testing the precision of brain areas stimulated by c-tDCS, e.g., in this case, comparing the outcomes of stimulating left vs. right M_1 or S_1 on a migraine brain; (b) using electrodes of equal size; (c) applying anode as the main polarity influencing the brain, and (d) comparing the present study protocol with a bipolar tDCS.

Conclusion

The results of the present study confirmed the positive effects of c-tDCS application on reducing the frequency, duration, and intensity of pain in migraine patients. Cathodal-tDCS application to the right primary motor or the right primary sensory cortex offers promising prophylactic and therapeutic outcomes for migraine patients.

Clinical implications

Applying 20 min of c-tDCS with a direct current of 1000 μA intensity over 22 sessions to the right primary motor or sensory cortex:

- reduces the measured aspects of migraine (pain characteristics) significantly.
- is a safe and convenient intervention.
- produces no short-term (beyond 1 h) or long-term undesirable side effects.

CRediT authorship contribution statement

Mohammad Dawood Rahimi: Conceptualization, Methodology, Data curation, Investigation, Project administration, Writing - original draft. **Javad Salehi Fadardi:** Funding acquisition, Conceptualization, Methodology, Supervision, Formal analysis, Writing - review & editing. **Morteza Saeidi:** Resources, Supervision, Validation. **Imanolla Bigdeli:** Resources, Supervision, Validation. **Rohollah Kashiri:** Resources, Supervision, Validation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.02.012.

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