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Prophylactic treatment in menstrual migraine: A proof-of-concept study

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ABSTRACT

The present study aimed to investigate the efficacy of repetitive cathodal direct current stimulation (rctDCS) over the visual cortex as a prophylactic treatment in patients with menstrual migraine. 20 female patients were recruited in this double-blind, placebo-controlled study and were assigned to receive either cathodal or sham stimulation. Over 3 menstrual cycles, tDCS with 2 mA intensity and 20 min duration was applied to the visual cortex of the patients, in 5 consecutive sessions 1–5 days prior to the first day of their menstruation. The primary endpoint of the study was the frequency of the migraine attacks at the end of the treatment period, however, additional parameters, such as the number of migraine related days and the intensity of pain were also recorded 3 months before, during and 3 months post-treatment. Visual cortex excitability was determined by measuring the phosphene thresholds (PTs) using single pulse transcranial magnetic stimulation (TMS) over the visual cortex.

Sixteen patients completed the study. A significant decrease in the number of migraine attacks ($p = 0.04$) was found in the cathodal group compared to baseline but not compared to sham ($p = 0.053$). In parallel the PTs increased significantly in this group, compared to the sham group ($p < 0.05$).

Our results indicate that prophylactic treatment with rctDCS over the visual cortex might be able to decrease the number of attacks in patients with menstrual migraine, probably by modifying cortical excitability.

1. Introduction

For migraine, prophylactic therapy is often recommended to patients suffering from a strong intense and/or a high frequency of attacks. Although a broad range of pharmaceutical options exists, there is an increasing interest toward non-pharmaceutical alternatives with reduced side-effects to common prophylactic medications (e.g. [21,50,54]).

Several studies have demonstrated the efficacy of transcranial magnetic (TMS) and direct current stimulation (tDCS) in the acute and prophylactic treatment of migraine [5,18,20,34,35,37,43,53,55]. The effect of these stimulation methods is based on influencing neuronal activity and therefore, presumably, they can also interfere with the occurrence of cortical spreading depression [33]. Studies have shown that migraine headache was diminished or stopped by application of two-pulses of TMS over the visual cortex or over the painful area [18,34].

Concerning tDCS there is evidence at the cellular level that anodal tDCS and cathodal tDCS affect the different neuronal compartments [45,46]. It was suggested that anodal tDCS hyperpolarizes the membrane potential in the apical dendritic regions and depolarizes it in the somatic region, whereas the cathodal stimulation has a reversed effect. The estimation of the stimulation's effect on cortical excitability in humans is mostly performed by measuring the amplitude of the motor-evoked-potentials (MEPs) induced by single-pulse TMS [42] and might not be transferred to other stimulation montages over non-motor cortical areas.

With regard to the prophylactic application of tDCS in migraine, Antal [5] and coworkers treated patients with episodic and chronic migraine using cathodal versus sham stimulation over the visual cortex. In the active treatment group a significant reduction in the duration of the attacks, the intensity of pain and the number of migraine-related days post-treatment was observed compared to the baseline period, whereas the frequency of the attacks remained constant. However, compared to the sham group, only the intensity of the pain was significantly less, in case of a migraine attack. Vigano et al. [55] also reported a preventive effect of a two-weekly session of tDCS in migraine, however using excitatory anodal stimulation over the visual cortex. Dasilva and colleagues found comparable results by applying anodal tDCS, in this instance, over the primary motor cortex (M1) [20].

Taken as a whole, the results of previous papers exploring the efficacy of transcranial stimulation in migraine treatment are somewhat contradictory. This is partly due to methodological factors, such as using diverse stimulation protocols on heterogeneous patient populations. The present study aimed to investigate the efficacy of tDCS in a uniform subtype group of patients with menstrual migraine. It is estimated that approximately 50% of women with migraine have an increased risk of

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experiencing migraine during the premenstrual phase [37]. Menstrual migraine includes menstrual-related migraine, which is defined as migraine attacks occurring on days −2 + 3 of menstruation in at least two out of three cycles as well as at other times during the cycle, and pure menstrual migraine, in which migraine occurs only in association with menstruation on or between days −2 + 3 [1,26,49]. The most plausible trigger for menstrual migraine is the decline in serum estradiol levels. Declines in magnesium levels in the serum or sensitization of nociceptors by prostaglandins, released from the endometrium may also contribute to the development of pain. Furthermore, the decrease in the activity of the inhibitory neurotransmitter systems might result in increased firing of the neurons and increased neuronal excitability. Acute and short or long term preventative therapies may be used for the treatment. However, menstrual migraine has been reported to be more disabling and less responsive to acute therapy than non-menstrual migraine [1]. Short term prophylactic therapies are applied for 4–8 days and include non-steroidal anti-inflammatory drugs, triptans and estrogen transdermal patches/gel. Continuous prophylactic therapies include hormonal treatments or beta-blockers, calcium channel blocker, tricyclic antidepressants and anticonvulsants, usually with lots of side effects [37].

While in these patients the appearance of the migraine attack is highly predictable, we hypothesized that repetitive applications of cathodal tDCS (rctDCS) that are expected to have an inhibitory effect [4,6], applied over the visual cortex as a prophylactic treatment before the onset of menstruation, would decrease the likelihood of the occurrence of the next migraine attack.

2. Methods

2.1. Patients

Twenty female patients with menstrual migraine were recruited into the study. Inclusion criteria were: that the diagnosis must meet the 2004 IHS criteria ([26], specific criteria for menstrual migraine are in the appendix A) for migraine without aura or migraine with aura; the duration of the disease must be at least 6 months. Patients with chronic health disorders, diagnosed neuropsychiatric disorders, pregnant or breast feeding, with a history of substance abuse or dependence, and with a history of neurological disorders other than migraine were excluded. Patients who had an implanted pacemaker or metallic hardware in the head or scalp (e.g. surgical clips) were not included in the study. Patients were advised to maintain the pain medication (in case of an attack) and contraception (that was started a minimum of 6 months before the enrollment into the study) during the whole study period. None of the patients were acute migraine medication abuser. During the study four patients, two from the sham and two from the active groups, dropped out (see Fig. 1. and Results section below). Sixteen patients completed the study (Table 1).

All aspects conformed to the Declaration of Helsinki; written informed consents were given by all study participants. The experimental protocol was approved by the ethics committee of the Medical Faculty of the University of Göttingen.

2.2. Experimental design

This study was a double-blind, placebo-controlled study. The primary endpoint of the study was the frequency of the migraine attacks, the secondary efficacy endpoint the number of migraine-related days (the number of days on which the patients had migraine-related symptoms). The study had three phases (Fig. 1.): (i) baseline period, consisting of 12-weeks in which the frequency of the migraine attacks was recorded, including the onset and duration of the pain and the number of migraine-related days and the type of analgesics taken in case of a migraine attack; (ii) a 12-week treatment period, consisting of 3 × 5 treatment sessions with either sham or cathodal tDCS (20 min) for 5 days before the expected onset of the menstruation; and (iii) a follow-up period of 12-weeks to further record the abovementioned parameters. Patients were asked to maintain a headache diary throughout the duration of the entire study period.

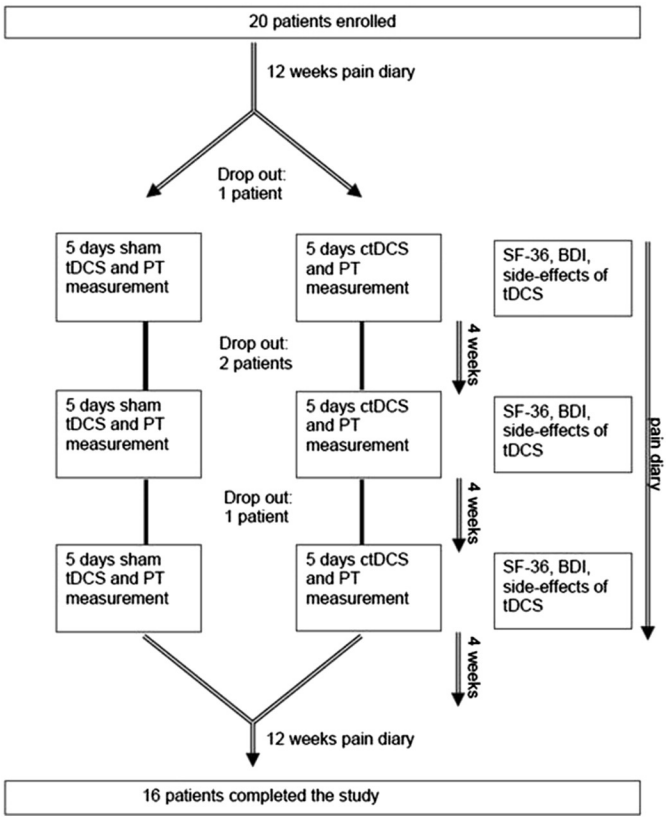

Fig. 1. Graphical sketch of the 9 month study period. The study included three phases, each consisting of 12 weeks. During the first period the frequency and the duration of the migraine attacks were documented. The subsequent phase consisted of the repeated application of a five-day cathodal or sham treatment. In a follow-up period the frequency and the duration of the migraine attacks were recorded. PT: phosphene threshold.

Table 1
The demographical characteristics and medical history of the patient group indicated using means and SDs.

	Cathodal	Sham
With aura	2	2
Without aura	6	6
Mean age (SD)	31,6 (6,2)	27,1 (4,4)
Mean duration in years (SD)	12,1 (5,1)	9,8 (6,5)
Mean number of attacks/year (SD)	14,7 (4,5)	13,9 (2,5)
Side(s) of pain		
One	7	6
Both	1	2
+ Family history	8	7
Medication		
ASS (Aspirin®)	1	1
Triptans	2	3
Ibuprofen	7	4
Paracetamol	2	3
Others	1	1
Contraception		
Oral	5	5
NuvaRing	1	2
Nicotin	1	3

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2.3. Transcranial direct current stimulation

The patients were enrolled to get treatment 'A' or 'B', (every second patient recruited was in the group B). The stimulators were coded by the coordinating investigator, who had no contact to the patients. The stimulation was applied either by an experimenter or by the patient at home, after being provided with detailed instructions and a training session in the department. Patients were instructed to perform the stimulation always during the same time of the day. Direct current was transferred by a saline-soaked pair of sponge electrodes (7 cm × 5 cm) and delivered using a battery-driven constant current stimulator (NeuroConn, Ilmenau, Germany). The cathode was placed over the Oz and the anode over the Cz electrode positions according to the 10–20 EEG system. Using this electrode montage parietal and occipital cortices show strong current densities in the range of 0.05–0.15 A/m^2 and they are stronger in medial than in lateral occipital cortex. According to a modeling study these electrode positions seems well suited for visual cortex stimulation [40]. A constant current of 2 mA intensity was applied for 20 min, including 20 s ramp-up and down phases. For sham stimulation, the electrodes were placed in the same positions as for cathodal stimulation, but the stimulator was turned off automatically after 30 s of stimulation. The patients and the investigator were blinded with regard to the type of tDCS applied. The patients were aware of the fact that they might receive either sham or real stimulation.

2.4. Phosphene threshold (PT) measurements

As a physiological index of cortical excitability PT measurements were acquired. Many studies have employed this metric as method to evaluate cortical excitability in visual studies (e.g. [9,10,15,16,24,31,39]). PT measurements were made before and 1–2 days after the tDCS sessions in order to determine the excitability of the visual cortex using a MagPro-Stimulator (Medtronic Functional Diagnostics, Skovlunde, DK butterfly coil: MC-B70, biphasic pulse). During the measurement patients were seated in a comfortable chair with armrests. The coil was first positioned 2 cm on the inion, with the handle pointing upwards. In order to find the lowest PT (the best individual position for stimulating) the coil was moved to the left and right in 1 cm steps. The optimal position was marked and measured using a measuring tape. After marking the recording position, the intensity of the stimulation was increased until over threshold and was slowly decreased in 5%-steps until the patients were unable to see a phosphene. At around threshold-level, the intensity of the stimulator was decreased and then increased again but in 1%-steps until the patients reported a visual sensation. This procedure was repeated twice and the intensity of the stimulation was recorded for each trial.

2.5. Questionnaires

2.5.1. Quality of life (SF-36)

The SF-36 is a self-administered survey, which contains 36 items clustered in eight dimensions. Item scores for each dimension are coded, summed and transformed to a scale ranging from "0" (worst possible health status) to "100" (best possible health status). Thus, higher values indicate a better evaluation of health. The health domains are: (1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality; and 8) general health problems [23].

2.5.2. Side effects

Since any potential adverse effects of this technique in a patient population are not yet fully known, the patients completed a questionnaire after each stimulation session. It contained rating scales for the presence and severity of headache, difficulties in concentrating, acute mood changes, visual perceptual changes, fatigue and discomforting sensations like pain, tingling, itching or burning under the electrodes during and after tDCS [44].

2.6. Statistical analyses

This trial is a proof-of-concept study providing first efficacy data. With regard to the primary and secondary endpoints a p-value of ≤ 0.05 was considered significant. All other analyses are considered exploratory and confidence intervals as well as p-values are reported without correction for multiple testing.

2.6.1. Characteristics of migraine attacks

With regard to the number of migraine attacks (primary endpoint) and migraine-related days (secondary endpoint) the data were not normally distributed, therefore a Mann–Whitney U test was used to compare data between the two groups and Wilcoxon-matched-pairs test to compare the mean values within groups. A p-value of ≤ 0.05 was considered significant. Data are given as mean ± SEM.

2.6.2. Phosphene thresholds

Repeated measures ANOVA was used to test for differences in PTs with the factors 'type of stimulation' (active and sham) and 'time' (before and after treatment in the first, second and third periods). Conditional on significant F-values, two-tailed paired-sample t-tests were used to characterize the main effects or interactions as revealed by the ANOVAs. A p-value of ≤ 0.05 was considered significant. Data are given as mean ± SEM.

2.6.3. Quality of life (SF-36)

Separate repeated measures ANOVAs were used to test for differences in the 8 domains of the test with the factors 'type of stimulation' (verum and sham) and 'time' (first, second and third periods). Conditional on significant F-values, two-tailed paired-sample t-tests were used to characterize the main effects or interactions as revealed by the ANOVAs. A p-value of ≤ 0.05 was considered significant. Data are given as mean ± SEM.

2.6.4. Side effects

The incidences of side-effects were coded in a binary system (no = 0, yes = 1) and the severities of the side-effects were rated using a numerical analogue scale (NAS) from one to five, one being very mild and five being of an extremely strong intensity of any given side-effect. The incidences and severities of the adverse effects were separately calculated during and after stimulation.

3. Results

During the study four patients, two from the sham and two from the active groups, dropped out due to different reasons (Fig. 1): one of them was due to the 'clicking' sound of the TMS machine discharging and the others could not integrate the stimulation in their daily activities. Finally, 16 women completed the study.

3.1. Primary efficacy endpoint: frequency of migraine attacks

During the three month treatment period, five patients had no or less attacks in the cathodal stimulation group and 2 subjects in the sham group. In the cathodal group the number of migraine attacks decreased compared to the sham group, however, this decrease was not significant ($Z_{adjusted} = -1.92$; $p = 0.053$), although a tendency toward having less attacks in the cathodal group was observed. There was no significant difference between the two groups at baseline ($Z_{adjusted} = 0.87$; $p = 0.38$) and after treatment ($Z_{adjusted} = -0.46$; $p = 0.64$).

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Nevertheless, within the cathodal but not in the sham group the number of migraine attacks was significantly reduced during the treatment period, when during-stimulation frequencies were compared to the baseline values ($Z = 2.02$; $p = 0.04$; sham: $Z = 1.34$; $p = 0.18$) (Fig. 2).

3.2. Secondary efficacy endpoint: migraine-related days

In case of the number of migraine related days, there was no significant difference between the two groups at baseline ($Z_{adjusted} = -1.86$; $p = 0.063$), during ($Z_{adjusted} = -0.89$; $p = 0.37$) and after treatment ($Z_{adjusted} = -0.32$; $p = 0.75$). Nevertheless, within the cathodal group the number of migraine related days was less compared to baseline, however, the difference was not significant (mean cathodal: 4.62 ± 1.6; mean sham: 6.12 ± 0.8; $Z = 1.86$; $p = 0.063$; sham $Z = 1.6$; $p = 0.11$) (Fig. 3). Unfortunately half of the patients did not give information with regard to the dose of the acute drugs taken during the migraine attacks, therefore the possible differences between the two groups concerning the amount of analgesic medication taken, could not be evaluated.

3.3. Other measurements

3.3.1. Phosphene thresholds

The repeated measures ANOVA revealed a main effect of stimulation ($F(1,14) = 7.56$, $p = 0.016$) and time ($F(1,14) = 4.4$, $p = 0.05$). A significant interaction between 'type of stimulation' and 'cycles' ($F(2,28) = 4.56$; $p = 0.02$) was also found. Cathodal tDCS produced a consistent increase in mean PTs (Fig. 4) in the second (before: $p = 0.03$; after: $p = 0.02$) and third (before: $p = 0.01$; after: $p = 0.006$) treatment months compared to the sham group.

3.3.2. SF-36

With regard to the SF-36 there was an improvement in several domains, however, independently from the type of the stimulation. There was only 1 domain (2, social interactions), in which a significant difference was observed between the two treatment groups (stimulation: $F(1,14) = 3.8$, $p = 0.05$; time: $F(2,28) = 3.6$, $p = 0.04$; interaction: $F(2,28) = 0.5$, $p = 0.6$)), nevertheless, in this case the sham stimulated group was better.

3.3.3. Adverse effects of tDCS

None of the patients terminated the stimulation, or required any medical intervention during or after tDCS. Eighteen patients completed the questionnaire. Table 2 summarizes the adverse effects experienced during (A) and after (B) stimulation, including 26 sham and 24 cathodal stimulation conditions. During cathodal stimulation a moderate tingling sensation was the most common adverse effect; it was reported by 83.3% of the cathodal stimulation sessions and by 53.8% during sham stimulation. Moderate itching was the second most frequent consequence, felt 70.8% during cathodal and 38.5% during sham stimulation.

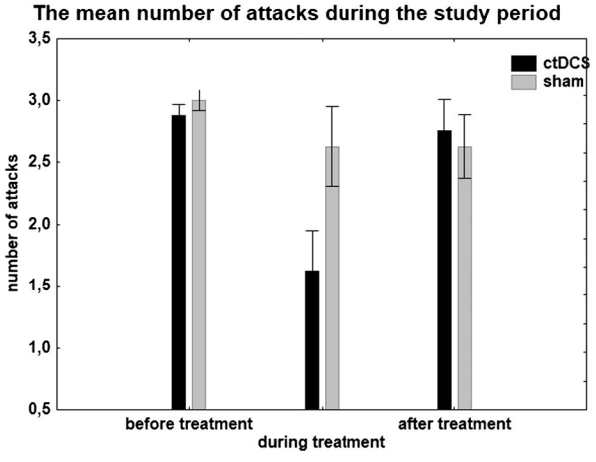

Fig. 2. The number of attacks before (12 weeks), during (12 weeks) and after (12 weeks) the treatment period in the cathodal and sham groups. Bars represent SEMs. In the cathodal group a significant decrease of the attacks were observed, compared to baseline.

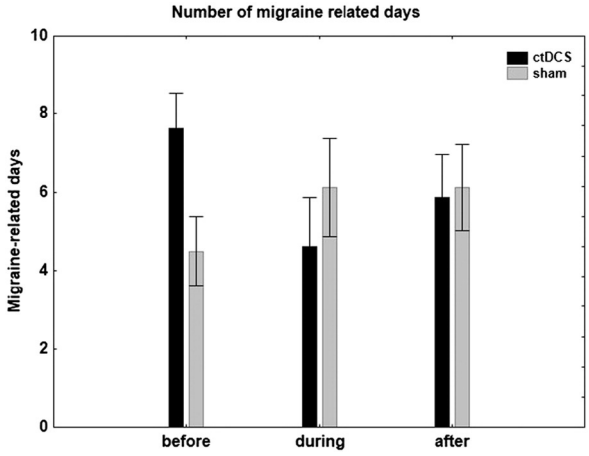

Fig. 3. The number of migraine-related days before (12 weeks), during (12 weeks) and after (12 weeks) the treatment period in the cathodal and sham groups. Bars represent SEMs.

4. Discussion

Our assumption, that inhibitory tDCS over the visual cortex could be an effective prophylactic therapeutic option by diminishing cortical excitability, was based on data suggesting that migraine is associated with higher neuronal excitability or responsiveness (e.g. [2,16,17,25,28,36,38]) and on previous results suggesting that cathodal stimulation can decrease the excitability of the visual cortex (for a review see [7]). Indeed, the main finding of this study is a significant reduction in the number of migraine attacks during the 3-month treatment period in the cathodal group, compared to baseline. The effect of cathodal stimulation did not last after the end of the 3-month treatment, suggesting that patients should repeat the stimulation in order to have a clinical benefit. Unfortunately, the primary endpoint between the two treatment groups was not significant, but a tendency toward experiencing less attacks in the cathodal group was observed ($p = 0.053$).

In menstrual migraine prophylactic therapy is frequently used during the perimenstrual period. Medications administered include nonsteroidal anti-inflammatory drugs, beta blockers, tricyclic antidepressants (for reviews see: [1,49]) and triptans [29]. Overall, all of these treatment options were more effective than placebo in the prevention of menstrual migraine, demonstrated in small clinical trials; however, the level of efficacy was only between 30 and 60% when examining different factors, e.g. when the reduction of migraine- related days was considered as primary endpoint. As tDCS is able to change cortical excitability [42] by modulating the resting membrane potential of targeted neurons, and therefore also altering the spontaneous firing rates of already active neurons [12,19], we hypothesized that the application of repetitive cathodal stimulation over the visual cortex, as a non-pharmaceutical method, might be a viable therapeutic alternative. Unfortunately it is not clear if the stimulation directly can act on migraine pathophysiological mechanisms or not. Alternatively, it might modify the activity of the brainstem through nociceptive pathways. It was suggested that a functional connection between the visual cortex and brainstem 2nd order nociceptors in spinal trigeminal nucleus exists. Therefore, an inhibition from the visual cortex to the brainstem might result in less pain during attacks [47].

In our previous study [5] a heterogeneous group of 30 migraine patients were treated using either cathodal or sham tDCS for 6 weeks applied over the visual cortex, delivered three times per week, at 1 mA

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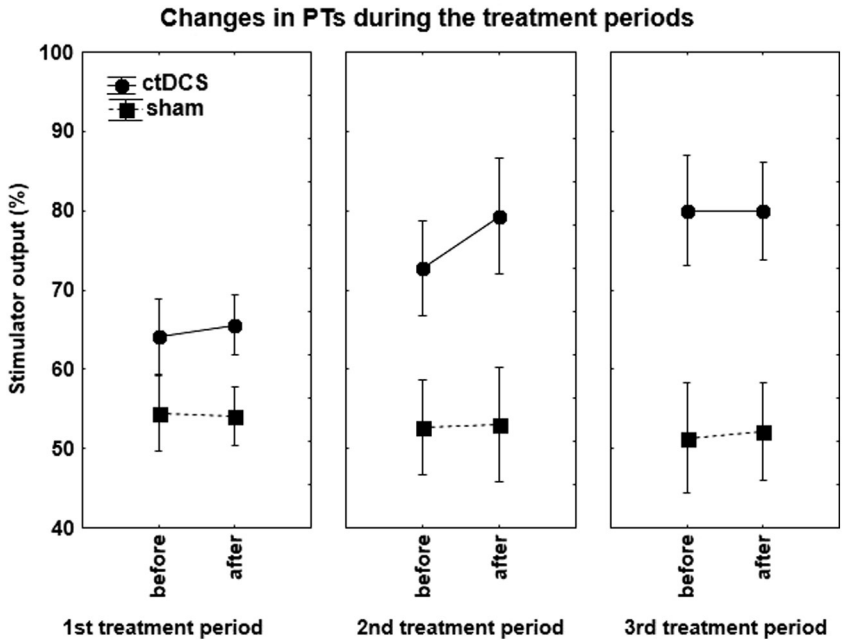

Fig. 4. Mean PT values before and after the tDCS treatments. In the cathodal group a significant treatment of PTs was observed. Bars represent SEMs.

intensity. Nevertheless, during the first 3 weeks both groups received only placebo stimulation. Patients treated with cathodal tDCS showed a significant reduction in the duration of migraine attacks, the intensity of pain and the number of migraine-related days post-treatment when compared to the baseline period, but not in the frequency of the attacks. However, compared to the sham group, only the intensity of the pain was significantly reduced post-stimulation. Therefore, in the present study we decided to increase the stimulation intensity to 2 mA and to also apply the stimulation on consecutive days.

Anodal stimulation of the M1 (mainly hand area) was also found to be effective in treating chronic migraine [11,20], supporting the idea of using excitatory stimulation protocols in chronic pain syndromes by stimulating the M1 (e.g.[8]). Although the position of the anodal electrode in our study was more posterior (Cz) the effect of concomitant excitatory stimulation could not be excluded. Interestingly, a recent clinical study on a small patient group ($n = 10$) [55] reported that anodal stimulation of the visual cortex (return electrode placed on the chin) was effective in the preventive treatment of episodic migraine. Besides the polarity of the stimulation and the electrode placement, the main difference between the abovementioned studies and our study was that we used a double-blind design, an approach that was not implemented in previous studies. However, the reported placebo effect in clinical studies treating migraine patients is around 30% (see e.g. [41, 48]), a factor that might dilute the effectiveness of a given stimulation condition.

In the cathodal group we observed a significant increase of visual cortical excitability as measured by single-pulse TMS. Although the perception of phosphenes is somewhat subjective, in recent years several studies on the visual cortex in healthy subjects and in patients, have used the intensity threshold at which phosphenes are elicited as a specific index of visual cortex excitability (e.g. [3,13,22,27,31,51,52,56]). The exact generation of phosphene perception is still under discussion, results suggest that PTs are not functionally analogous to motor-evoked potentials following TMS over M1 but more to conscious perception of visual stimuli, nevertheless occurring within an earlier time window [52]. Unfortunately, it was not possible to measure the cortical excitability in the different phases of the menstrual cycle of the patients, therefore we could not evaluate if the fluctuation of PTs [3,14] was eventually reduced by the stimulation.

The number and magnitude of the reported side effects were generally low. Interestingly, in the sham group a higher incidence of fatigue during and after treatment was observed. This raises the question, as to whether this classical (most often applied) electrode montage and stimulation protocol is able to ameliorate fatigue in general or whether the patients experienced less fatigue while they suffered less from migraine. Further studies are required to clarify this issue.

The limitations of this study should also be discussed. First, this small clinical trial was a proof-of-concept study; our sample size might not have been large enough to detect more characteristics associated with a positive effect of rctDCS (e.g. changes in the duration of the pain associated with the migraine attacks, use of rescue medication). Furthermore, we did not apply corrections for multiple testing that might increase the type-I error rate. However, with regard to clinical studies including a small number of patients, it has been suggested that for the global test comparing the primary and secondary endpoints across the two treatment groups, a p-value of less than 20% (two-sided) is considered an indication of a possible treatment effect and would warrant further investigation in future trials [32], which is definitely the case in this proof-of-concept study. Second, our patients might have favored alternative, non-pharmacological migraine treatments, which are not uncommon for patients with migraine and chronic pain, and therefore they might have a positive anticipation for tDCS treatment and its outcomes. Indeed, we observed improvements in the rating scales and overall outcomes in two patients, who received placebo rctDCS. Third, we have only tested one electrode montage and intensity; other paradigms varying these factors might be more effective in migraine treatment. Fourth, the focality of stimulation using electrodes of this size was probably quite low. In a recent computational modeling study, the predicted current flow in multiple cortical and subcortical regions associated with migraine pathophysiology showed that significant electric fields were generated not only in targeted cortical regions but also in the insula, cingulate cortex, thalamus, and brainstem regions [20]. Furthermore, recent papers suggest that in the motor and cognitive domains the variability to tDCS is higher, than it was reported previously [30,57,58] E.g. it have been demonstrated that the modulation of corticomotor excitability through tDCS in healthy participants is variable such that only 40–70% of healthy subjects respond to anodal tDCS with increased corticomotor excitability. Nevertheless, concerning the

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Table 2
Adverse effects of rctDCS recorded during (A) and after (B) the stimulation; values refer to the number of applied stimulation sessions (26 sham and 24 cathodal sessions).

A

	Pain			Tingling		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	2	8,33	1,5 +/− 0,5	20	83,33	1,75 +/− 0,69
Sham	6	23,07	1,83 +/− 1,46	14	53,84	2,07 +/− 0,79
	Itching			Burning		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	17	70,83	1,94 +/− 0,99	5	20,83	2,2 +/− 0,97
Sham	10	38,46	2,8 +/− 0,6	7	26,92	1,42 +/− 1,04
	Fatigue			Nervousness		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	0	0	0	0	0	0
Sham	4	15,38	2 +/− 1,73	2	7,69	2 +/− 0
	Headache			Changes in visual perception		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	3	12,5	1,66 +/− 0,94	1	4,16	1 +/− 0
Sham	1	3,84	5 +/− 0	1	3,84	4 +/− 0
	Unpleasantness			Changes in concentration abilities		
	N	%	MI +/− SD	N	%	
Cathodal	3	12,5	1 +/− 0	1	4,16	
Placebo	6	23,07	2 +/− 1,52	5	19,23	

MI = middle intensity

B

	Pain			Tingling		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	0	0	0	8	33,33	2 +/− 0,86
Sham	2	7,69	2,5 +/− 1,5	2	7,69	2 +/− 0
	Itching			Burning		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	11	45,83	2,45 +/− 1,23	1	4,16	1 +/− 0
Sham	4	15,38	1,75 +/− 0,43	4	15,38	2 +/− 1,73
	Fatigue			Nervousness		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	0	0	0	0	0	0
Sham	5	19,23	2,6 +/− 1,2	1	3,84	4 +/− 0
	Changes in concentration abilities			Headache		
	N	%	MI +/− SD	N	%	MI +/− SD
Cathodal	0	0	0	4	16,66	2 +/− 0,70
Sham	2	7,69	2 +/− 1	2	7,69	3 +/− 1
	Nausea			Emesis		
	N	%	MD (h) +/− SD	N	%	MH +/− SD
Cathodal	0	0	0	0	0	0
Sham	2	7,69	2,5 +/− 1,5	1	3,84	1 +/− 0
	Increased mood			Sensation of cold		
	N	%	MD (h) +/− SD	N	%	MD (h) +/− SD
Cathodal	0	0	0	3	12,5	1,3 +/− 0,47
Sham	1	3,84	4 +/− 0	2	7,69	3 +/− 2
	Other abnormalities (stronger concentration abilities, Paresthesia at the tongue, Vertigo)			Anxiety		
	N	%		N	%	
Cathodal	6	25		0	0	
Sham	4	15,38		1	3,84	

visual cortex no data are available with regard to this issue. Finally, the SF-36 questionnaires showed a tendency toward improvements in several categories, however, independent from the type of stimulation applied. It is possible that this type of questionnaire is not sensitive enough to detect tDCS induced changes on the long-term behavioral level. The application of Migraine Disability Assessment (MIDAS) questionnaire might be more suitable for this purpose.

In summary, although the primary endpoint of this study (frequency of the migraine attacks) was not significant between the two treatment groups, within the cathodal group a possible treatment effect was observed suggesting that rctDCS applied over the visual cortex could be an option for menstrual migraine prophylaxis. The advantage of applying rctDCS prophylaxis is that patients are less likely to experience unwanted side-effects, than when using conventional drug treatments. The data is encouraging with regard to the reduction in migraine-related days, an outcome, which makes the application of rctDCS a promising candidate for further studies in larger clinical populations, not only for the prophylactic treatment of migraine, but also for the spectrum of migraine-related disturbances. Future studies including more patients should also investigate the correlation between cortical excitability fluctuations (e.g. phosphene thresholds) and changes in clinical outcomes. These measurements could be important markers of how effective the treatment sessions were and they could also give us insights on the mechanisms of ctDCS over visual cortex.

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Disclosures

The authors have no conflicts of interest.

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