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Long-term prophylactic efficacy of transcranial direct current stimulation in chronic migraine. A randomised, patient-assessor blinded, sham-controlled trial



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ABSTRACT

Objective: To assess the prophylactic effect of anodal tDCS of the left motor cortex in patients with resistant chronic migraine (CM) and its long-term maintenance.

Methods: In a patient-assessor blinded, sham-controlled trial, 36 patients were randomized to receive anodal tDCS (active group, $n = 18$) or sham tDCS (sham group, $n = 18$). The studied population was characterized by a previous failure of at least 3 classes of preventive drugs and a mean duration of migraine history of 26 years. The tDCS procedure consisted of an induction phase of 5 consecutive daily sessions (week 1) followed by a maintenance phase of 1 weekly session during the next 4 weeks and two bimonthly sessions in the next month, for a total of 11 sessions during 2 months. Anodal tDCS was delivered at 2 mA intensity for 20 min over the left motor cortex. The primary endpoint was the reduction in the monthly number of migraine attacks from baseline to each period of follow-up (months 1, 2, 3, 5) between the active and sham groups.

Results: The monthly number of migraine attacks expressed as the percentage of reduction from baseline was significantly reduced in the active versus the sham group, from the end of first month ($-21\% \pm 22$ vs. $-2\% \pm 25$, $p = 0.019$) to the end of follow-up (3-month post-treatment) ($-32\% \pm 33$ vs. $-6\% \pm 39$, $p = 0.011$). At this time, the rate of responders, defined as a reduction of the monthly number of migraine attacks $\geq 30\%$ from baseline, was significantly higher in the active group than in the sham group (50% vs. 14%, $p = 0.043$).

Conclusion: Our results show a marked prophylactic effect of anodal tDCS of the left motor cortex in resistant CM extending several months after the stimulation period, and suggest that this neuromodulatory approach may be part of the prophylactic alternatives available for CM.

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Abbreviations: CM, Chronic migraine; tDCS, transcranial direct current stimulation; a-tDCS, anodal tDCS; rTMS, repetitive transcranial magnetic stimulation; HIT-6, Headache Impact Test–6; MIDAS, Migraine Disability Assessment Scale; SF-12, 12-item Short-Form Health Survey questionnaire; HADS, Hospital Anxiety and Depression Scale; CGI-I, Clinical Global Impression Improvement; rmANOVA, repeated measures analyses of variance; LMM, linear mixed-effect model.

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1. Introduction

Migraine is considered chronic when people “have 15 or more headache days per month for more than 3 months, with at least 8 of those days meeting criteria for migraine” (International Classification of Headache Disorders, 2018) [1]. Chronic migraine (CM) is the most common form of chronic daily headache and affects approximately 2% of the adult population in Western countries [2]. The severe reduction of life quality due to CM is directly correlated with the frequency of migraine attacks and the resistance to prophylactic treatments for migraine. Since CM may result in absenteeism from work and exclusion from daily, family and social activities, its impact in terms of direct and indirect costs at the individual and societal level is substantial [3].

In CM, central sensitization or long-term changes in brain plasticity may alter the modulatory systems of nociception [4–10]. These alterations have led to develop, for prophylactic purpose, invasive and non-invasive neuromodulation techniques such as occipital nerve stimulation (ONS), repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) [11–17]. ONS involves a surgical implantation of electrodes and pulse generator by a specialized team, while rTMS requires costly equipment and iterative hospital sessions for the patients. Compared to these two techniques, tDCS is a low-cost, easy-to-perform and well tolerated non-invasive technique that can be implemented at home. In practice, tDCS corresponds to the delivery of a weak electric direct current to the cerebral cortex, usually performed by means of two large electrodes (anode and cathode) placed on the scalp. In the context of chronic pain, the usual target of cortical stimulation since the early 90s is the motor (precentral) cortex [18], either of the hemisphere contralateral to pain in case of focal or lateralized pain or of the left (dominant) hemisphere in case of more diffuse or non-lateralized pain. Using anodal tDCS (a-tDCS) delivered to this motor (precentral) cortical target, significant analgesic effects have been demonstrated in various chronic pain conditions [19–21], in particular fibromyalgia [22] and neuropathic pain secondary to spinal cord injury [23] or multiple sclerosis [24], although the clinical benefit was considered controversial [25,26].

The mechanisms of action of tDCS are not yet fully understood [27]. Based on tDCS-induced changes in motor cortex excitability [28], anodal stimulation was initially thought to produce an excitatory effect through membrane depolarization, while an inhibitory effect could be produced by cathodal stimulation through membrane hyperpolarization. However, tDCS effects on brain circuitry are more complex, depending on the direction of current flow (tangential or radial) and the neuronal compartment impacted (somatodendritic axis or distal axon terminals) [29], and therefore on polarity, size, or placement of the electrodes, on the targeted cortical site or the duration of stimulation [27]. Moreover, it is now assumed that tDCS can play a neuromodulatory role in the central nervous system by acting on various systems of neurotransmission,

e.g., GABAergic, glutamatergic, dopaminergic, serotonergic, or cholinergic, leading to its potential clinical effect [30]. As acknowledged in a recent review [31], a majority of studies exploring the impact of tDCS on synaptic neurotransmission have been performed using a-tDCS of the left motor cortex and investigated GABA changes. These studies suggested decreased GABAergic activities at the origin of plastic changes following a-tDCS. However, after-effects of a-tDCS of the left motor cortex were rather found to be related to long-term potentiation of glutamatergic synaptic transmission via NMDA receptors [32].

In migraine, changes in cortical excitability were associated with alteration of glutamatergic neurotransmission and homeostatic plasticity [33]. Therefore, there is a rationale to propose a-tDCS of the left motor cortex as a therapeutic approach in migraine. Some encouraging results have been published [12,16,34–36]. However, the current level of evidence of the therapeutic effect of tDCS protocols in migraine remains low [19]. Most of these studies were based on short-term follow-up, small and heterogeneous populations and various stimulation protocols. Notably, only a few controlled studies have investigated the use of tDCS in patients with CM [8,37,38], while patients with CM and episodic migraine were mixed in other studies [39,40]. Also, the primary objective of our randomized sham-controlled study was to assess the long-term prophylactic effect of a-tDCS delivered to the left motor cortex on the frequency of migraine attacks in a homogeneous population of patients with long-lasting resistant CM.

2. Material and methods

2.1. Study design

The study was approved on December 14, 2013 by the Institutional Review Board of Sud-Est V, Grenoble, France (N° 6705). Written informed consent was obtained from all participants prior to enrolment. The study was registered with clinicaltrials.gov (NCT02120326).

This patient-assessor blinded, randomized sham-controlled trial with two parallel arms (active versus sham a-tDCS) was conducted between May 5, 2014 and December 18, 2019 at the Pain Centre of the Grenoble Alpes University Hospital. The study consisted of 3 phases (Fig. 1): an assessment of the frequency of migraine attacks for one month before treatment with a-tDCS (Baseline); after randomization, a 2-month period of active or sham a-tDCS, including an induction phase and a maintenance phase for a total of 11 sessions (Month 1, 2); a 3-month follow-up post-treatment phase (Month 3, 4, 5). Patients were evaluated at 5 scheduled visits: at one month before treatment (Day –30), at the end of the first month of treatment (Day 30), at the end of the two months of treatment (Day 60), at one month post-treatment (Day 90), and at 3 months post treatment (Day 150).

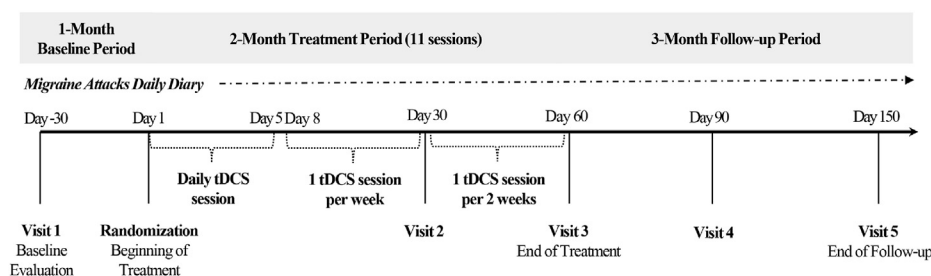


Fig. 1. Protocol design: interventions and assessment time points. Assessments at each visit: Headache Impact Test (HIT-6); Migraine Disability Assessment (MIDAS); Patient Clinical Global Impression (CGI); the short form 12-health survey questionnaire (SF-12); Hospital Anxiety and Depression Scale (HADS).

2.2. Study population

Patients with CM were included if they met the following criteria: age between 18 and 85 years; diagnosis of CM [1]; disease duration ≥ 12 months; ≥ 8 migraine attacks in the past month; absence of improvement by at least 3 different well-conducted prophylactic treatments [41], which corresponds to a “resistant migraine” according to a recent international consensus [42]; no change in drug treatments during the last month; no introduction of other prophylactic treatment for migraine until the end of the follow-up study.

Patients were not included if they were pregnant or breastfeeding women, or if they had intracranial ferromagnetic material or implanted device, a history of drug addiction, epilepsy, or neuropsychiatric comorbidities, which could interfere with outcome assessments.

A total of 36 patients were included in the study and randomized to a tDCS treatment condition.

2.3. Randomization

After the baseline period, patients were randomly allocated in a 1:1 ratio into two groups using a secure Web-based random number generator (Research Electronic Data Capture system) to select permuted blocks, with a random block size. Patients and assessors were blinded to the allocated group. The investigator who performed the tDCS sessions had no access to the assessments.

2.4. tDCS procedure

The tDCS protocol consisted of an induction phase of 5 consecutive daily sessions during the first week (week 1) followed by a maintenance phase of 1 weekly session during the next 4 weeks and two bimonthly sessions in the next month, for a total of 11 sessions.

Stimulation was performed using a Starstim neurostimulator (Neuroelectrics, Barcelona, Spain) with saline-soaked surface sponge electrodes (35 cm²). The site of stimulation was determined according to the International 10–20 EEG System. The anode was placed on C3 to target the hand area in the left motor cortex and the cathode was placed on FP2, i.e. the right supraorbital area. A constant current of 2 mA intensity was applied for 20 min.

For the sham stimulation, the electrodes were similarly placed but the current was stopped 30 s thereafter: the subject felt the initial itching sensation but no stimulation was continued. This sham procedure was applied in most previous tDCS studies [28,43] and considered the most usual placebo approach in a technical guide of tDCS [44].

2.5. Clinical outcomes/endpoints

From the baseline (Day –30) to the last follow-up assessment (Day 150), patients used a diary at home to record the following information about migraine attacks: date, duration, pain intensity using a 0–10 numerical rating scale (0 = no pain to 10 = worst pain imaginable), and use of medication. A migraine attack was defined according to the International Classification of Headache Disorders (2018) [1], including criteria of intensity (moderate or severe) and duration of attack (at least 30 min).

The primary endpoint was the reduction in the average number of migraine attacks per month from the baseline period to each period of follow-up (Month 1–5) between the active and sham a-tDCS groups. The number of migraine attacks was calculated on diary recordings over 30 consecutive days.

For secondary endpoints, patients completed the following self-administered questionnaires at each visit: the HIT-6 to assess the impact of headache on the overall quality of life, ranging from 36 to 78 with larger scores reflecting greater impact [45]; the MIDAS to assess the number of days of disability due to migraine, graded I–III “minimal to moderate disability” (0–20 days) or IV “severe disability” (more than >20 days) [46]; the SF-12 to assess the health-related quality of life across two dimensions (physical and mental component), using scores from 0 to 100 with a higher score indicating a better quality of life [47]; and the HADS to assess symptoms of anxiety and depression, ranging from 0 to 21 for each subscale with higher scores indicating worse symptoms [48]. The overall effect of the stimulation was estimated by the patients according to the 7-point CGI-I scale, ranging from 1 (very much improved) to 7 (very much worsened) compared to the pre-treatment baseline period [49]. An “improvement rate” was calculated as the percentage of patients improved.

Finally, we evaluated the responder rate at the end of follow-up (3-month post-treatment), according to a reduction $\geq 30\%$ from baseline regarding the number of migraine attacks. Other secondary criteria of response were measured: a reduction $\geq 30\%$ in the use of triptan medication; a reduction ≥ 6 points on the HIT-6 score or ≥ 5 days on the MIDAS according to the minimum clinical relevance accepted for these questionnaires [50,51].

2.6. Blinding integrity assessment

The effectiveness of blinding was assessed at the end of the follow-up by asking patients to indicate which treatment they thought they had received (“active stimulation”, “sham stimulation”, or “do not know”).

2.7. Sample size

The sample size of the population was calculated on the basis of an average of 8.2 ± 3.7 migraine attacks per month in CM patients [52]. Assuming a two-sided alpha risk of 0.05, a power of 80% and a correlation of 0.7 or more between repeated measurements, the enrollment of two equally sized groups (30 patients per group) could detect a 50% reduction in the number of migraine attacks per month at the end of the treatment in the active group versus 20% reduction in the sham group [53] (NQuery Advisor® 7.0).

The study was initially intended to be bicentric, but one centre failed to start the study and recruit patients. The study therefore took place in a single centre and the decision to stop the study was taken without any prior review of the data, only due to a recruitment challenge after a 5-year inclusion period. This issue reduced the sample size, but did not affect the study, which was designed to have independent recruitment and randomization for each center. Thus, a total of 36 patients were enrolled in the study.

2.8. Statistical analysis

Continuous data are expressed as mean \pm standard deviation (SD) or median (25th–75th centiles), while categorical data are expressed as numbers and percentages. Comparisons were conducted on an intention-to-treat basis by using the Chi-square or Fisher's exact test, Student's t-test or Wilcoxon-Mann-Whitney test.

Efficacy analyses (active versus sham a-tDCS) were conducted independently for each endpoint. For continuous variables, changes from baseline to the end of the follow-up were analysed using 2-way repeated measures analyses of variance (rmANOVA) with “Time” as within-subjects factor and “Group” as between-subjects factor and the calculation of “Time-by-Group” interaction. For

diary data (migraine attack frequency and analgesic medications), the factor “Time” was a 6-level variable (Baseline, Month 1, 2, 3, 4, 5); for questionnaire data (HIT-6, MIDAS, SF12 and HADS), the factor “Time” was a 5-level variable (Day -30, 30, 60, 90, 150). Bonferroni’s post-hoc tests for comparisons to baseline were performed for significant main effects or interaction. Between-group differences from the baseline period to each time point of the follow-up period were compared using unpaired Student’s t-test or Wilcoxon-Mann-Whitney test. Effect sizes of group differences were calculated using Cohen’s *d*. A linear mixed-effect model (LMM) that accommodates missing data using missing-at-random and missing-not-at-random assumptions [54] was implemented as a sensitivity analysis to assess for heterogeneity of the factor “Group” across “Time”. Models included “Time”, “Group”, “Time-by-Group” interaction as fixed factors and subject as random effect. Because gender, age and migraine attack number at baseline might differ between groups (p -value < 0.15), these variables were included as fixed covariates at each of the models. The most appropriate covariance structure for the residual correlation matrix was selected. For categorical variables, we used the Chi-square or Fisher’s exact test to compare between-group differences at each time point of the follow-up period.

Data were analysed using Stata 16.0 software (StatCorp, College Station, TX, USA). The statistician was blinded to the treatment groups. A two-sided P value < 0.05 was considered statistically significant and no adjustments for multiple testing were performed.

3. Results

3.1. Flowchart of the study

Of the 36 patients who were randomly assigned to a study group (18 in the active group and 18 in the sham group), migraine diary was lost by two patients (one in each group) (Fig. 2). Therefore, only 34 patients were included in the intent-to-treat (ITT) population for the primary outcome. Finally, 28 patients (14 in the active group and 14 in the sham group) completed the 5-month follow-up assessment for the primary outcome. Of these, one patient in each treatment group showed protocol deviation because they changed migraine prophylactic treatment during the study. These patients were excluded from the analysis for the period following treatment change. Two patients in each treatment group stopped completing the migraine diary and were excluded from the analysis for the period of missing data.

3.2. Baseline demographics and clinical characteristics

The demographics and baseline characteristics of the 36 included patients are shown in Table 1. A greater percentage of male patients and a higher age were found in the active group versus the sham group: 44% vs 11% ($P = 0.026$) and 54.5 ± 10.6 vs. 46.1 ± 14.1 years ($P = 0.051$), respectively.

3.3. Primary outcome: evolution of the number of migraine attacks per month

Whether expressed as an absolute difference or as a percentage with respect to the baseline, a larger reduction in the number of migraine attacks per month was found in the active group versus the sham group throughout the follow-up (rmANOVA time-by-group interaction $F(5,145) = 3.22$, Greenhouse-Geisser $P = 0.0198$; LMM time-by-group interaction $F(5,146.4) = 3.29$, $P = 0.008$). Pairwise comparisons showed a significant decrease in the number of migraine attacks per month expressed as the

percentage of reduction from baseline in the active group versus the sham group from the end of the first month of treatment ($-21.0\% \pm 21.6$ vs. $-1.5\% \pm 24.5$, effect size = -0.85 , $P = 0.019$) to the end of follow-up (3 months post-treatment) ($-31.9\% \pm 33.1$ vs. $-5.6\% \pm 39.4$, effect size = -1.03 , $P = 0.011$) except at ‘Month 2’ time point (Table 2). Post-hoc tests of rmANOVA showed a significant reduction in the number of migraine attacks per month at all time points compared to baseline in the active tDCS group (Month 1: $P = 0.034$; Month 2: $P = 0.016$; Month 3: $P = 0.021$; Month 4: $P < 0.01$; Month 5: $P < 10^{-3}$) but not in the sham tDCS group (Fig. 3). Overall, the tDCS sessions were very well tolerated and there were no serious side effects to report.

3.4. Secondary outcomes: self-administered questionnaires

No significant differences between the two treatment groups were observed regarding the scores of the different questionnaires used in this study (HIT-6, MIDAS, SF-12, HAD) during or after the period of stimulation (Table 3). Regarding CGI-I, statistical results revealed no significant difference in the improvement rate between groups at all time points (data not shown).

3.5. Secondary outcomes: impact on treatment of migraine attacks

A significant reduction in the consumption of triptans was found in the active group versus the sham group at ‘Month 4’ time point (2 months post-treatment) compared to baseline (-2.1 ± 3.7 vs. 2.5 ± 4.7 , effect size = -1.07 , $P = 0.010$). No significant difference between groups was observed in the consumption of non-opioids or weak opioids during or after the stimulation period (Table 3).

3.6. Analyses in terms of responders

According to the primary criterion of response (a reduction $\geq 30\%$ from baseline regarding the number of migraine attacks per month), the rate of responders was significantly higher in the active group versus the sham group at ‘Month 5’ time point (3 months post-treatment) (50% vs. 14%, $\text{Chi}^2 = 4.09$, $P = 0.043$) (Fig. 4). Moreover, the rate of responders with a reduction $\geq 50\%$ of the number of migraine attacks per month tended to be higher in the active group versus the sham group: 36% vs 7% respectively ($\text{Chi}^2 = 3.39$, $P = 0.065$). A tendency towards a better efficacy of active versus sham a-tDCS was also observed for two secondary criteria of response: a reduction ≥ 6 points on the HIT-6 score (36% vs 8%, $\text{Chi}^2 = 3.06$, $P = 0.080$); a reduction ≥ 5 days on the MIDAS (75% vs 42%, $\text{Chi}^2 = 2.74$, $P = 0.098$) (Fig. 4).

On the other hand, we did not find any significant difference between the responders and non-responders (defined on the reduction of the number of migraine attacks per month) regarding their various clinical characteristics at baseline, failing to reveal any predictive value of these characteristics (Table 4).

3.7. Blinding integrity

At the end of the follow-up period, most patients were not able to indicate which treatment they had received: “active stimulation”, “sham stimulation” or “do not know” was the response given by 3, 2, and 9 patients, respectively, in the active group and by 5, 4, and 6 patients, respectively, in the sham group ($\text{Chi}^2 = 1.73$, $P = 0.42$). The responses to the blinding integrity questionnaire showed the reliability of blinding in both groups.

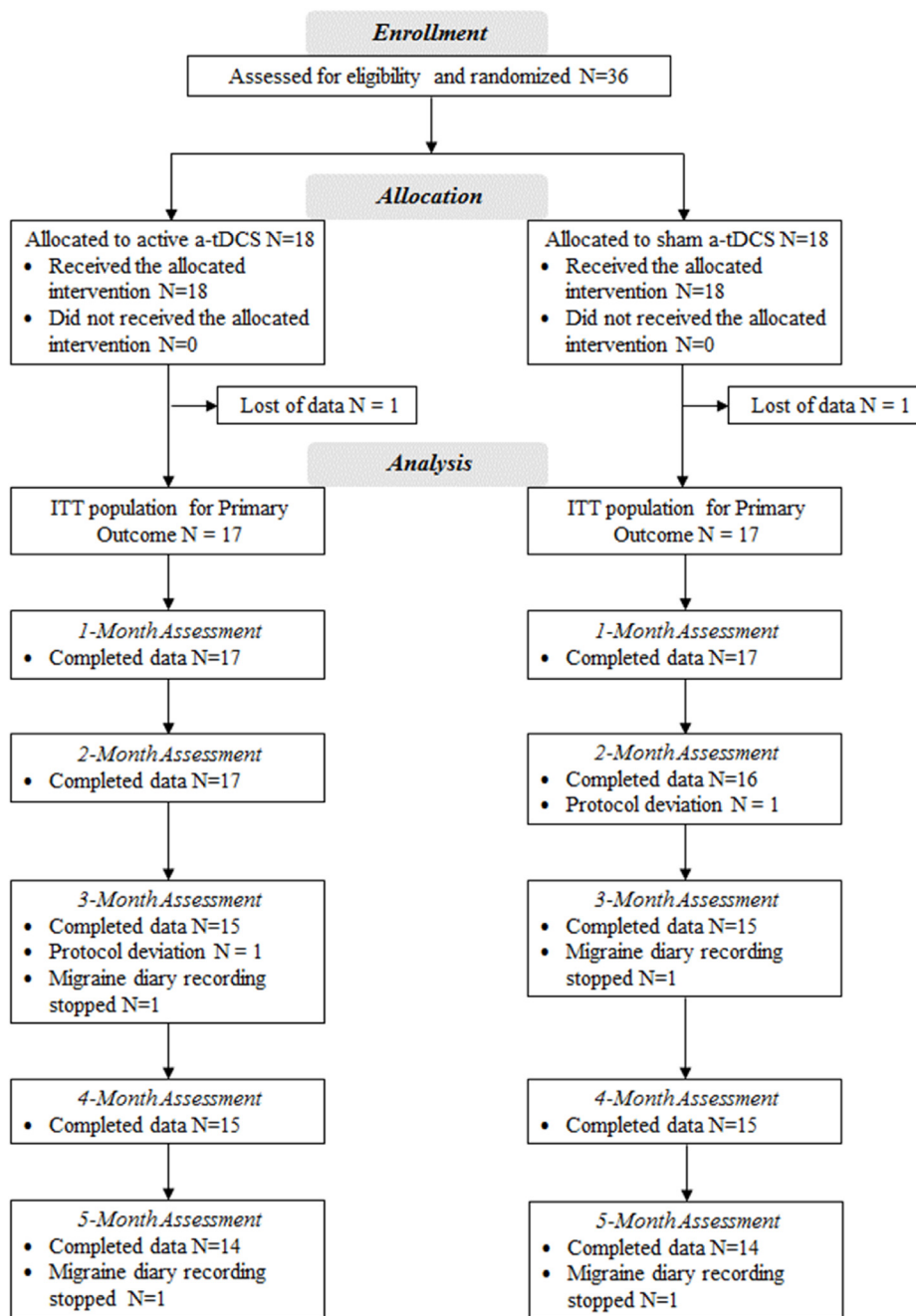


Fig. 2. Participant flow diagram. ITT (intent-to-treat) population included all randomized participants who received at least 1 session of the study treatment and recorded baseline migraine attacks.

4. Discussion

This study assessed the prophylactic efficacy of a-tDCS of the left motor cortex in patients with resistant CM and its long-term maintenance. The strengths of this study were the design of the study (sham-controlled trial and blinded assessors and patients) and the homogeneity of the patient population (resistance to at least 3 different prophylactic treatments and long disease duration ≥ 12 months, 25.9 years on average).

To our knowledge, this is the first sham-controlled study evaluating the long-term reduction in the frequency of migraine attacks using a-tDCS of the left motor cortex in the context of well-defined resistant CM with a very long disease duration. In designing this

study with an induction phase and a maintenance phase, we were inspired by the protocols using rTMS in the long-term treatment of chronic pain [55] and our observations in this domain [56,57]. In the present study, a significant decrease in the number of migraine attacks per month was observed from one month of treatment in the active group. This positive effect was even more pronounced at the end of follow-up (3 months post-treatment). Post-hoc tests of rmANOVA also showed a significant reduction in the number of migraine attacks per month at all time points compared to baseline in the active group, but not in the sham group. Thus, a significant prophylactic effect of a-tDCS treatment was observed, including early and long-lasting beneficial effects.

Table 1
Baseline characteristics of patients according to the allocated group.

	Total (n = 36)	Active a-tDCS (n = 18)	Sham a-tDCS (n = 18)	p-value
Age (years), mean (SD)	50.3 (13.0)	54.5 (10.6)	46.1 (14.1)	0.051
Female, n (%)	26 (72%)	10 (56%)	16 (89%)	0.026
Disease history				
Time (years) since migraine onset, mean (SD)	25.9 (14.6)	27.8 (13.5)	24.1 (15.7)	0.444
History of prophylactic medication use:				
Current use, n (%)	24 (67%)	10 (56%)	14 (78%)	0.157
Number of prophylactics used, median (IQR)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	0.580
Type of prophylaxis used:				
Amitriptyline, n (%)	29 (81%)	14 (78%)	15 (83%)	0.999
Other antidepressant, n (%)	8 (22%)	5 (28%)	3 (17%)	0.691
Topiramate, n (%)	22 (61%)	10 (56%)	12 (67%)	0.494
Other antiepileptic, n (%)	10 (28%)	5 (28%)	5 (28%)	0.999
Oxetorone, n (%)	23 (64%)	10 (56%)	13 (72%)	0.298
Beta-blocker, n (%)	21 (58%)	12 (67%)	9 (50%)	0.310
Other antihypertensive, n (%)	7 (19%)	4 (22%)	3 (17%)	0.999
Other, n (%)	4 (11%)	3 (17%)	1 (6%)	0.603
Usual treatment of migraine attack:				
Triptan, n (%)	32 (89%)	15 (83%)	17 (94%)	0.603
Non-opioid analgesic, n (%)	33 (92%)	17 (94%)	16 (89%)	0.999
Paracetamol, n (%)	18 (50%)	11 (61%)	7 (39%)	0.182
NSAIDs, n (%)	27 (75%)	16 (89%)	11 (61%)	0.121
Weak opioid analgesic, n (%)	20 (56%)	12 (67%)	8 (44%)	0.180
Disease characteristics during the month prior to tDCS				
Number of migraine attacks/month, mean (SD)	16.2 (7.8)	18.29 (7.9)	14.12 (7.2)	0.118
Analgesic drug consumption (number of doses):				
Triptan, median (IQR), n of patients	7.0 (4.0, 11.0) 30	5.5 (4.0, 13.0) 14	7.5 (3.5, 10.5) 16	0.662
Non-opioids, median (IQR), n of patients	10.0 (4.0, 16.0) 30	10.0 (2.0, 14.0) 15	8.0 (5.0, 19.0) 15	0.607
Weak opioids, median (IQR), n of patients	8.0 (3.0, 23.0) 19	4.0 (3.0, 36.0) 11	8.5 (0.0, 13.5) 8	0.433
Clinical scores at the inclusion visit, 1 month pre-tDCS				
HIT-6, mean (SD)	65.2 (4.3)	65.2 (2.9)	65.1 (5.5)	0.947
MIDAS, mean (SD)	65.8 (48.6)	68.7 (48.6)	62.6 (50.3)	0.738
SF-12 Physical component scale, mean (SD)	34.4 (9.5)	34.4 (10.0)	34.4 (9.1)	0.987
SF-12 Mental component scale, mean (SD)	36.0 (11.3)	36.9 (9.8)	34.9 (13.1)	0.625
HADS-anxiety, mean (SD)	9.7 (4.6)	9.6 (4.7)	9.9 (4.7)	0.852
HADS-depression, mean (SD)	8.7 (4.5)	9.2 (4.5)	8.2 (4.7)	0.549

Abbreviations: ITT, intention to treat; SD, standard deviation; IQR, interquartile range; NSAIDs, Non-steroidal anti-inflammatory drugs; tDCS, transcranial direct current stimulation; HIT-6, Headache Impact Test–6 (36–78); MIDAS, Migraine Disability Assessment Scale (0–270); SF-12, 12-item Short-Form Health Survey questionnaire (0–100); Physical and Mental subscales; HADS, hospital anxiety and depression scale (0–21); Anxiety and Depression subscales.

Table 2
Primary outcome: changes in the monthly number of migraine attack.

Number of migraine attacks per month	Active a-tDCS	Sham a-tDCS	Between-group difference mean (95% CI)	Between-group effect size	Between-group p-value
Baseline to Month 1					
Absolute change	n = 17 –3.3 (3.9)	n = 17 –1.4 (4.0)	–1.9 (–4.7 to 0.8)	–0.49	0.082
Percentage change	–21.0 (21.6)	–1.5 (24.5)	–19.6 (–35.7 to –3.4)	–0.85	0.019
Baseline to Month 2					
Absolute change	n = 17 –3.6 (4.7)	n = 16 –0.3 (4.7)	–3.3 (–6.6 to 0.0)	–0.71	0.050
Percentage change	–20.1 (26.6)	2.6 (33.9)	–22.8 (–44.4 to –1.1)	–0.75	0.039
Baseline to Month 3					
Absolute change	n = 15 –3.73 (3.63)	n = 15 –2.20 (4.8)	–1.5 (–4.7 to 1.6)	–0.36	0.331
Percentage change	–27.4 (28.4)	–11.8 (38.1)	–15.7 (–40.8 to 9.4)	–0.46	0.211
Baseline to Month 4					
Absolute change	n = 15 –5.07 (4.4)	n = 15 0.0 (6.2)	–5.1 (–9.1 to –1.1)	–0.94	0.015
Percentage change	–35.6 (30.4)	2.2 (44.1)	–37.8 (–66.2 to –9.5)	–1.00	0.011
Baseline to Month 5					
Absolute change	n = 14 –5.1 (4.9)	n = 14 0.1 (7.5)	–5.3 (–10.2 to –0.4)	–0.83	0.036
Percentage change	–31.9 (33.1)	5.6 (39.4)	–37.5 (–65.8 to –9.2)	–1.03	0.011

Data are expressed as absolute and percentage changes from baseline (mean ± SD). A negative change within groups means improvement. Between-group differences were calculated as active minus sham tDCS group results: a negative difference favors the active tDCS group. SD, standard deviation; CI, confidence interval. Between-group effect size based on Cohen's d.

Finally, the rate of responders ($\geq 30\%$ reduction) at 5 month follow-up (3 months post-treatment) was significantly higher in the active group versus the sham group regarding the number of migraine attacks per month and tended to be higher regarding two secondary outcome measures: the HIT-6 and the MIDAS.

4.1. Prophylactic treatments of CM

The first-line prophylactic treatments of CM are based on medications [58–62]. The anticonvulsant topiramate has been recently recommended as the first-line prophylactic treatment for CM in French guidelines [59], because of the highest level of

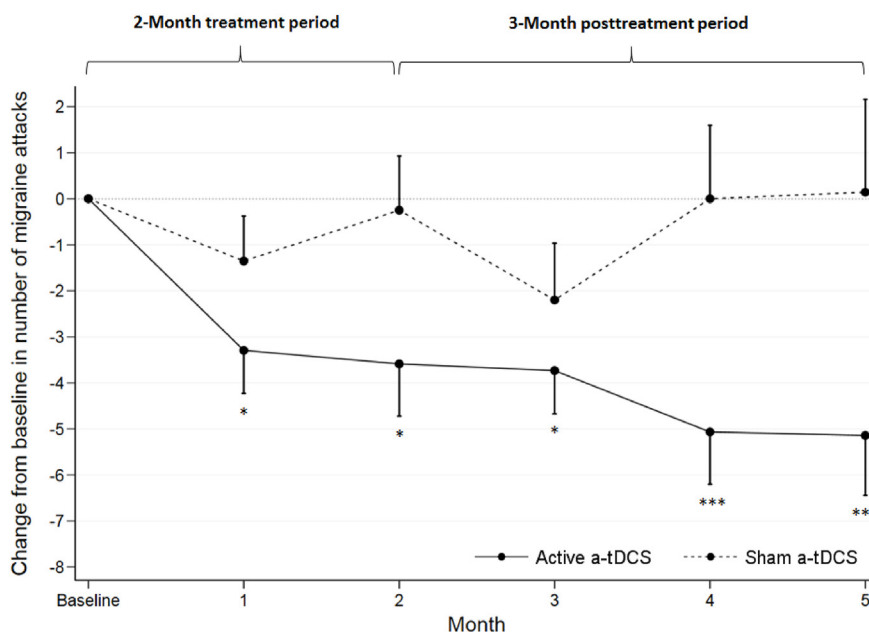


Fig. 3. Change from baseline in the monthly number of migraine attacks. The line graph represents the mean values with standard errors bars on modified intention-to-treat population. Bonferroni's post-hoc tests compared to baseline: * $p < 0.05$, ** $p < 0.01$, *** $p < 10^{-3}$.

evidence of efficacy, notably based on a large, multicenter, controlled clinical trial [63]. In this benchmark study, the efficacy of topiramate (100 mg/day) was compared with placebo for the treatment of 306 patients with CM. Topiramate intake resulted in a significant reduction by 11% at 3 month follow-up in the mean number of migraine attacks or migrainous headache days per month from baseline compared to placebo ($-37.1\% \pm 34.8$ vs $-26.0\% \pm 40.8$, $P = 0.012$). In the present study, a significant reduction in the monthly number of migraine attacks at 5 month follow-up in the active group versus the sham group was also found, but this reduction was of 26.4% ($-31.9\% \pm 33.1$ vs $-5.6\% \pm 39.4$, $P = 0.011$). Although the sample population studied was small, our findings indicate that a-tDCS of the left motor cortex may be a prophylactic treatment for CM.

In chronic pain, it is recommended to report the percentage of patients responding with a reduction $\geq 30\%$ on a pain measure, as reflecting a clinically important (at least moderate) difference in a pain treatment trial [64]. In the present study, the response to treatment was defined as a reduction $\geq 30\%$ from baseline regarding the number of migraine attacks per month. At the end of follow-up (3-month post-treatment), the rate of responders was significantly higher following active versus sham a-tDCS (50.0% vs. 14.3%). For comparison, in the large, multicenter, controlled clinical trial on the efficacy of topiramate mentioned above, this criterion of response (set at $\geq 25\%$ reduction rather than $\geq 30\%$) was met by 68.6% vs 51.6% in the active and placebo groups, respectively [65]. We have no explanation for the fact that the placebo response is much lower in our study than in the previous study with topiramate, but it appears not to be due to a break in blinding integrity (referring to our assessment of the reliability of blinding). Thus, the efficacy of a-tDCS of the left motor cortex seems to be comparable to topiramate used as first-line prophylactic treatment in CM. The efficacy of a-tDCS observed in the present study is also comparable to that recently reported in studies considering the impact of botulinum toxin type A (BTA) or monoclonal antibodies against CGRP (mAbs) on the number of headache days as primary endpoint, reporting an effect size and responder rate of 50% [62,66–69]. Thus, the efficacy of a-tDCS of the left motor cortex seems to be at least similar to all

medications currently used as prophylactic treatment for CM and also for resistant CM, an observation that must to be confirmed by larger studies.

4.2. Previous tDCS studies in migraine

Previously published studies aimed at treating headache by using tDCS are very heterogeneous in terms of stimulation setup, patient clinical profile, sample size, and follow-up duration [13,35]. In the literature, we found 14 sham-controlled tDCS studies performed in migraine patients. Six studies were based on cathodal tDCS of the occipital cortex [70–75] and 5 studies were based on anodal tDCS of the left motor cortex or the motor cortex contralateral to the most frequent migraine side [8,37,39,76,77]. Other studies included the cathodal tDCS of the right sensorimotor cortex [40,78], the cathodal tDCS of a scalp region identified by thermographic examination [38], or the stimulation of the dorsolateral prefrontal cortex [37,74]. The majority of these tDCS studies concerned patients with episodic migraine. Two publications addressed chronic medication overuse headache [74,77]. Finally, typical CM was only addressed in 5 studies. In two of these studies, patients with CM were mixed with patients with episodic migraine without any distinction in the results provided [39,40]. Therefore, only 3 studies were specifically conducted in patients with typical CM. In one study, the tDCS protocol was based on the cathodal stimulation of a scalp region identified by thermographic examination without any further detail on the corresponding cortical anatomical area [38]. In a second study, only 6 patients received active stimulation (anodal tDCS of the motor cortex) for a total of 12 sessions, with no follow-up after treatment [37]. Finally, only one study can be compared to the present study. In that study, only 8 patients with CM received active anodal tDCS over the motor cortex region contralateral to the dominant pain side for a total of 10 sessions within 4 weeks [8]. In the present study, 17 patients with CM received active anodal tDCS over the left motor cortex for a total of 11 sessions within 8 weeks, with a follow-up of 3 months post-treatment. In the study of DaSilva et al., 2012 [8], the results obtained with a-tDCS of the motor cortex were compared to a sham

Table 3
Secondary outcomes.

	Active a-tDCS	Sham a-tDCS	Between-group effect size	Between-group p-value	F (Time by Simulation)
Self-administered questionnaires					
HIT-6					
BL to D30	−2.9 (3.5)	−2.2 (5.8)	−0.13	0.747	$F_{4,109}^A = 1.60, P = 0.180$
BL to D60	−3.3 (3.7)	−1.9 (5.6)	−0.30	0.432	$F_{4,71.2}^L = 1.42, P = 0.236$
BL to D90	−1.3 (2.6)	−0.9 (3.9)	−0.11	0.781	
BL to D150	−5.1 (6.6)	−1.1 (5.4)	−0.66	0.098	
MIDAS					
BL to D30	−5.4 (56.3)	−20.2 (44.0)	0.29	0.507	$F_{4,93}^A = 0.55, P = 0.697$
BL to D60	−6.5 (62.5)	2.5 (46.8)	−0.16	0.691	$F_{4,94.1}^L = 0.55, P = 0.696$
BL to D90	3.8 (32.7)	3.5 (52.9)	−0.01	0.989	
BL to D150	−20.9 (44.8)	2.8 (40.3)	−0.56	0.187	
SF-12 Physical component scale					
BL to D30	3.6 (7.9)	2.2 (8.6)	0.17	0.661	$F_{4,108}^A = 0.58, P = 0.678$
BL to D60	4.0 (7.5)	3.2 (7.1)	0.10	0.785	$F_{4,108}^L = 0.53, P = 0.714$
BL to D90	2.8 (7.0)	4.8 (8.4)	−0.26	0.496	
BL to D150	3.4 (5.2)	2.0 (11.3)	0.17	0.668	
SF-12 Mental component scale					
BL to D30	−1.1 (9.0)	1.3 (8.2)	−0.27	0.485	$F_{4,108}^A = 1.23, P = 0.302$
BL to D60	4.3 (13.7)	−1.3 (9.9)	0.46	0.225	$F_{4,108.4}^L = 1.10, P = 0.361$
BL to D90	2.2 (10.9)	−0.5 (10.0)	0.26	0.491	
BL to D150	5.2 (11.1)	−0.9 (9.0)	0.60	0.141	
HADS-Anxiety					
BL to D30	−1.2 (3.3)	−0.8 (2.2)	−0.15	0.702	$F_{4,108}^A = 0.74, P = 0.565$
BL to D60	−1.0 (3.6)	−1.6 (2.1)	0.19	0.619	$F_{4,107.7}^L = 0.74, P = 0.564$
BL to D90	−0.9 (3.5)	−2.2 (3.3)	0.37	0.332	
BL to D150	−1.3 (3.3)	−0.7 (2.6)	−0.19	0.613	
HADS-Depression					
BL to D30	−0.9 (4.3)	0.0 (3.0)	−0.23	0.555	$F_{4,108}^A = 0.66, P = 0.623$
BL to D60	−2.3 (4.3)	−0.1 (4.0)	−0.54	0.173	$F_{4,108.3}^L = 0.75, P = 0.558$
BL to D90	0.0 (2.6)	0.4 (4.0)	−0.12	0.761	
BL to D150	−1.3 (3.2)	0.2 (4.1)	−0.39	0.308	
Treatment of migraine attacks					
Triptan					
BL to M1	−1.7 (3.9)	0.1 (4.5)	−0.42	0.259	$F_{5,127}^A = 1.84, P = 0.125$
BL to M2	−0.6 (5.7)	1.3 (5.2)	−0.35	0.354	$F_{5,126.7}^L = 1.63, P = 0.156$
BL to M3	−1.8 (3.4)	−0.1 (3.1)	−0.52	0.185	
BL to M4	−2.1 (3.7)	2.5 (4.7)	−1.07	0.010	
BL to M5	−1.4 (3.5)	0.5 (3.6)	−0.53	0.208	
Non-opioid analgesics					
BL to M1	−2.3 (5.7)	−1.0 (5.7)	−0.23	0.526	$F_{5,126}^A = 0.90, P = 0.486$
BL to M2	−3.1 (5.9)	−2.8 (5.4)	−0.06	0.870	$F_{5,125.8}^L = 0.39, P = 0.852$
BL to M3	−3.1 (5.1)	−3.3 (6.8)	0.03	0.943	
BL to M4	−4.1 (4.7)	−3.5 (6.3)	−0.12	0.751	
BL to M5	−6.8 (23.9)	−3.3 (6.8)	−0.20	0.649	
Weak opioid analgesics					
BL to M1	−4.9 (10.7)	−2.0 (5.7)	−0.32	0.455	$F_{5,82}^A = 0.90, P = 0.390$
BL to M2	−5.0 (10.3)	−0.8 (5.3)	−0.50	0.252	$F_{5,61.9}^L = 0.95, P = 0.454$
BL to M3	−0.3 (6.5)	−2.6 (5.4)	0.38	0.439	
BL to M4	1.1 (12.7)	0.1 (8.3)	0.09	0.847	
BL to M5	−8.1 (19.5)	−0.3 (5.8)	−0.52	0.252	

Data are expressed as absolute change from baseline (mean ± SD). A negative change within groups means improvement except for SF-12. SD, standard deviation; BL, Baseline; D, Day; M, month; HIT-6, headache impact test-6 (36–78); MIDAS, migraine disability assessment scale (0–270); SF-12, 12-item Short-Form Health Survey questionnaire (0–100); Physical and Mental subscales; HADS, hospital anxiety and depression scale (0–21): Anxiety and Depression subscales. A Repeated measures analyses of variance. LLinear mixed-effect models.

group of only 5 patients and showed only a trend for significant reduction of pain intensity of the migraine attacks at the end of the a-tDCS protocol. At a delayed follow-up of 3 months, the reduction in the intensity of pain and the duration of migraine episodes was significant. This could be considered as a preliminary study with no reported data on the effect of a-tDCS on the number of migraine days. The present study goes much further and shows the significant therapeutic beneficial effects on the number of migraine attacks in resistant CM.

Other studies found a significant reduction in the number of headache/migraine days from one to 6 months following 3 to 20 sessions of a-tDCS of the motor cortex in episodic migraine or chronic medication overuse headache [39,76,77]. Interestingly, one

study showed that a prolonged treatment of 22 sessions (over 10 weeks) of monopolar cathodal tDCS of the right motor cortex (with the anode on the left arm) could also reduce the number of migraine attacks for a very long period, up to 12 months, compared to a sham protocol [40]. In contrast, a shorter protocol of 5 sessions of anodal or cathodal tDCS of the right motor cortex was ineffective to improve the long-term efficacy of an acute withdrawal protocol in patients with chronic medication overuse headache [78].

4.3. Duration and prediction of effects

As with rTMS, the analgesic effects of a single session of tDCS are short-lived and session repetition is essential to achieve lasting

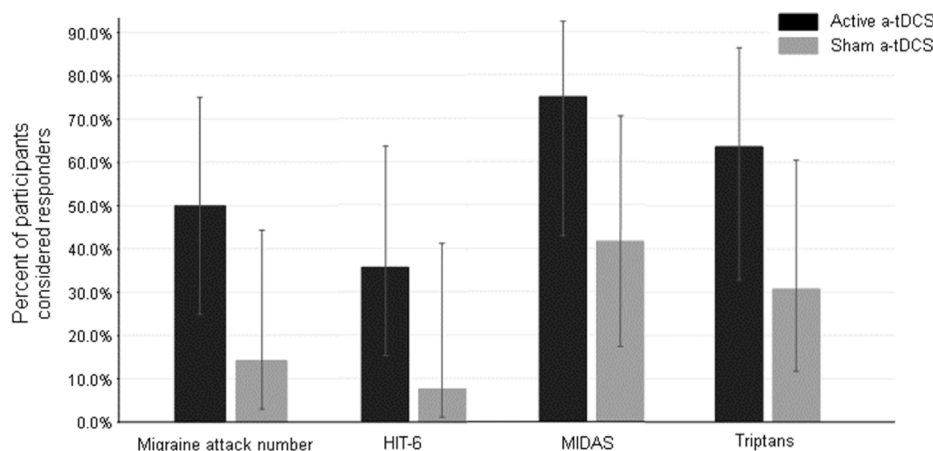


Fig. 4. Responder rates at the end of the study (3 months post-treatment) from baseline. Responder status: number of migraine attacks: reduction of $\geq 30\%$; HIT-6: a score reduction of ≥ 6 points; MIDAS, a score reduction of ≥ 5 points; use of triptan: reduction of $\geq 30\%$. The errors bars represent 95% confidence intervals.

relief through a cumulative effect. A recent meta-analysis showed that treatment with tDCS repeated over several days for a period ≥ 4 weeks could be effective in reducing the intensity and duration of migraine attacks [35]. Sustained and repeated tDCS sessions can thus induce cumulative and lasting neuroplastic changes in the cerebral cortex [79].

Regarding the duration of efficacy, a problem to be solved is the potential synergistic effect with drug treatments. For example, one study supported an add-on prophylactic effect of cathodal tDCS delivered to various cortical targets as an adjunct to topiramate, with a marked reduction in the frequency of migraine attacks in patients treated for CM [38]. In the present study, there was no difference between responders and non-responders regarding the concomitant use of prophylactic drugs, as well as in the consumption (number of doses) of analgesic drug to treat attacks. However, the synergistic effects between tDCS and drugs have not been well studied. In any case, the potential prophylactic long-term effect of preventing migraine attacks by tDCS appears encouraging in terms of routine clinical application, although intriguing compared to the rather less prolonged therapeutic effects of tDCS reported in other pathological conditions [19].

Unfortunately, the analysis of responder profile in the present study did not reveal any predictor of therapeutic response (cf Table 4), possibly due to a lack of statistical power due to the small sizes of patient subgroups.

4.4. Mechanisms of action

The article of DaSilva et al., 2012 [8], included a modeling study which supports a diffuse effect of anodal tDCS from the motor cortex site of stimulation to various deeper structures of the pain neuromatrix, such as cingulate gyrus, insular cortex, thalamic nuclei, and brainstem. Neuroimaging investigations of CM-induced brain plasticity, although sparse, have shown various types of changes, including a bihemispheric increase in the regional cerebral blood flow in the primary somatosensory cortex, which was positively correlated with headache attack frequency [80]. During migraine attacks, there are also various changes in thalamo-cortical connectivity, notably involving the motor cortex [10]. Therefore, there is a rationale for the use of a-tDCS of the motor cortex as an analgesic therapy in resistant CM, as one type of chronic pain syndrome among others. Indeed, as reported in various reviews [18,81–83], beyond a direct modulation effect on the underlying neuronal fibers running superficially in the precentral gyrus, a-tDCS of the motor cortex is also able to modulate neuronal activities in many cortical and subcortical structures distant from the site of stimulation. These structures can play an important role in the control of nociception, such as the thalamocortical pathways. Stimulation of the motor cortex can also lead to strengthening or restoring the descending inhibitory controls of nociceptive information transmission. Finally, brain structures involved in the

Table 4
Baseline characteristics of responders versus non-responders.

	Responders (n = 7)	Non-responders (n = 7)	p-value
Age (year), mean (SD)	55.0 (5.2)	52.9 (11.2)	0.654
Female, n (%)	4 (57%)	4 (57%)	0.999
Time (months) since migraine onset, mean (SD)	33.3 (10.7)	26.4 (15.2)	0.348
Current use of prophylactic medication, n (%)	4 (57%)	4 (57%)	0.999
Migraine attacks frequency, mean (SD)	15.7 (7.3)	22.4 (8.3)	0.135
Analgesic drug consumption (number of doses):			
Triptan, median (IQR)	5.5 (4.0, 9.0)	4.5 (4.0, 8.0)	0.810
Non-opioids, median (IQR)	7.0 (2.0, 14.0)	12.0 (2.0, 14.0)	0.775
Weak opioids, median (IQR)	3.5 (3.0, 23.0)	28.0 (12.0, 57.0)	0.166
HIT-6, mean (SD)	64.5 (3.4)	66.0 (2.3)	0.365
MIDAS, mean (SD)	53.7 (58.7)	69.5 (38.4)	0.592
SF-12 Physical component scale, mean (SD)	39.3 (14.0)	30.7 (6.4)	0.175
SF-12 Mental component scale, mean (SD)	40.8 (9.4)	32.0 (10.4)	0.140
HADS-anxiety, mean (SD)	8.9 (2.6)	11.7 (6.4)	0.295
HADS-depression, mean (SD)	7.7 (4.7)	11.4 (4.7)	0.164

SD, standard deviation; IQR, interquartile range; HIT-6, Headache Impact Test–6 (36–78); MIDAS, Migraine Disability Assessment Scale (0–270); SF-12, 12-item Short-Form Health Survey questionnaire (0–100); Physical and Mental subscale; HADS, hospital anxiety and depression scale (0–21); Anxiety and Depression subscales.

cognitive and affective aspects of pain, such as the cingulate, prefrontal, and orbitofrontal cortices, can also be modulated, via action on various neurotransmitter systems. All these mechanisms remain to be studied regarding the specific effect of a-tDCS of the left motor cortex in patients with CM.

4.5. Limitations

Several limitations should be recognized. First, the sample size was smaller than originally calculated for optimal statistical power. Therefore, some estimates may not have followed the statistical constraints necessary to show significant results. As mentioned above, this may explain the lack of any predictor of therapeutic response, possibly due to decreased statistical power.

Second, imprecision remains as to the location of the cortical region stimulated by a-tDCS. Although the placement of the anode was centered on the motor cortex, this site was defined as C3 using the International 10–20 EEG System and not by means of individual anatomical mapping using image-guided navigation, for example. In addition, since the electrode used was a disc with a radius <3.5 cm, this means that the electrode covered the premotor region rostrally (the premotor cortex being 3–3.5 cm anterior to the “motor hotspot” [84]) and the primary somatosensory region caudally. However, as usual in the literature, this tDCS montage was described as primarily targeting the motor cortex throughout the article.

A third limitation is about the understanding of the mechanisms of action of a-tDCS of the left motor cortex on the reduction of the number of migraine attacks. As mentioned above, these mechanisms remain speculative, although the long-term lasting effects argue for a plasticity-induction protocol. However, whether plasticity was induced by an increase or a decrease of cortical excitability remains to be determined. Indeed, a-tDCS is usually considered an excitatory protocol, but this varies according to timing-dependent effects of homeostatic plasticity. For example, the behavioral effects of a-tDCS on motor learning depend whether a-tDCS is applied concurrently or prior to the motor task, reflecting the influence of homeostatic interactions on GABAergic synaptic changes due to the stimulation [85]. The polarity of the electrode also plays a role, since cathodal but not anodal tDCS was found to restore the normal facilitatory response to high-frequency rTMS in patients with migraine, counteracting homeostatic mechanisms of cortical hypo-responsivity [86].

4.6. Suggestions for future research

The limitations described above should be the basis for future research to better understand and define the place of tDCS in the treatment of CM.

In a recent narrative review, it was concluded that the data on the prophylactic efficacy of tDCS in CM were conflicting [16]. This has already been discussed previously, and the positive results of the present study can be explained by the homogeneity of our population, despite the limitation of the sample size. Multicenter sham-controlled trials using the same stimulation parameters are needed to confirm the present results, given the difficulties in performing large single-center studies.

Second, although the motor cortex appears to be a promising target, questions remain open about which hemispheric side to stimulate (left, contralateral to the dominant migraine side, or even bilateral). The value of the motor cortex also remains to be compared with alternative cortical targets, such as the occipital cortex. Finally, alongside conventional bipolar montages, multisite (multifocal) tDCS is under development and is yielding interesting results [87–89]. This targeting question is one of the most

important challenges in the use of tDCS as a therapeutic strategy and relies on a better understanding of the brain networks to be stimulated and how to stimulate them to improve a pathological neurological condition.

Third, with regard to the understanding of the mechanisms of action, a major issue will be to study the effects of a-tDCS of the motor cortex on the alterations of cortical excitability which are known to exist in migraine patients [90,91]. Cortical excitability changes can be assessed in particular by neurophysiological techniques, such as non-invasive transcranial stimulation protocols, even concerning the influence of homeostatic plasticity processes [92,93]. The goal of future studies will be to determine what excitability changes are induced by tDCS of the motor cortex (especially according to the polarity of the stimulating electrode) in patients with CM and to see if these changes are correlated with clinical effects, such as the reduction of migraine attacks.

Finally, the place of tDCS alongside other neuromodulation techniques, such as transcutaneous electrical stimulation of the supra-orbital or occipital nerves, transcutaneous auricular or cervical stimulation of the vagus nerve, or high-frequency rTMS of the motor or the prefrontal cortex [13,17,94], remains to be confirmed for the prophylactic treatment of migraine. The advantage of tDCS relies also upon its safety and very good tolerance, leading to the fact that its acceptance by patients is potentially better than drugs treatments.

However, some constraints of tDCS should be mentioned, including the need for iterative sessions, although the number and timing of sessions needed to induce significant and prolonged clinical effects remain to be determined. In this context, the development of the at-home use of tDCS [75,95] constitutes an interesting and costless alternative to be addressed.

In responders, a-tDCS of the left motor cortex may help reduce drug consumption, thereby avoiding polypharmacy and its side effects, including drug addiction and chronic medication overuse headache. This aspect also deserves future studies, as well as the interest of tDCS as a preventive tool to avoid the evolution of resistant CM towards “refractory migraine”, defined as CM not improved by at least 5 different and well-conducted prophylactic treatments. Medico-economic studies will be also essential to assess the cost-efficacy of tDCS in a medical environment, particularly in comparison with the newly proposed prophylactic but costly treatments, such as BTA and anti-CGRP mAbs.

5. Conclusion

Our study shows the prophylactic efficacy of a-tDCS of the left motor cortex in the treatment of CM, including several months of lasting effects. However, the place of tDCS remains to be evaluated in the therapeutic armamentarium of CM, in particular as an alternative or in combination with prophylactic drug treatments and not only as a last resort in severe forms of patients with CM, who already have significant impact on mood and quality of life. The use of tDCS could therefore be an interesting therapeutic strategy to prevent the evolution of CM towards a refractory form. Larger controlled trials are needed to confirm the efficacy showed in the present study, and to identify predictive factors that may influence the clinical response to tDCS.

CRedit authorship contribution statement

Hasan Hodaj: Conceptualization, Methodology, Investigation, Validation, Project administration, Data curation, Writing – original draft, Writing – review & editing. **Jean-François Payen:** Supervision, Writing – original draft, Writing – review & editing. **Gerard Mick:** Conceptualization, Writing – review & editing. **Laurent**

Vercueil: Conceptualization, Writing – review & editing. **Enkelejda Hodaj:** Methodology, Formal analysis, Data curation, Visualization. **Anne Dumolard:** Investigation, Data curation. **Bénédicte Noëlle:** Investigation, Data curation. **Chantal Delon-Martin:** Supervision, Project administration. **Jean-Pascal Lefaucheur:** Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia* 2018;38:1–211. <https://doi.org/10.1177/0333102417738202>.
- [2] Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. *Headache* 2011;51:77–83. <https://doi.org/10.1111/j.1526-4610.2011.01954.x>.
- [3] Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, et al. Migraine: epidemiology and systems of care. *Lancet* 2021;397:1485–95. [https://doi.org/10.1016/S0140-6736\(20\)32160-7](https://doi.org/10.1016/S0140-6736(20)32160-7).
- [4] Burstein R. Deconstructing migraine headache into peripheral and central sensitization. *Pain* 2001;89:107–10. [https://doi.org/10.1016/S0304-3959\(00\)00478-4](https://doi.org/10.1016/S0304-3959(00)00478-4).
- [5] DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. *Neurology* 2007;69:1990–5. <https://doi.org/10.1212/01.wnl.0000291618.32247.2d>.
- [6] Chiapparini L, Ferraro S, Grazi L, Bussone G. Neuroimaging in chronic migraine. *Neuro Sci* 2010;31(Suppl 1):S19–22. <https://doi.org/10.1007/s10072-010-0266-9>.
- [7] Sprenger T, Borsook D. Migraine changes the brain: neuroimaging makes its mark. *Curr Opin Neurol* 2012;25:252–62. <https://doi.org/10.1097/WCO.0b013e3283532ca3>.
- [8] DaSilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache* 2012;52:1283–95. <https://doi.org/10.1111/j.1526-4610.2012.02141.x>.
- [9] Su M, Yu S. Chronic migraine: a process of dysmodulation and sensitization. *Mol Pain* 2018;14. <https://doi.org/10.1177/1744806918767697>.
- [10] Amin FM, Hougaard A, Magon S, Sprenger T, Wolfram F, Rostrup E, et al. Altered thalamic connectivity during spontaneous attacks of migraine without aura: a resting-state fMRI study. *Cephalalgia* 2018;38:1237–44. <https://doi.org/10.1177/0333102417729113>.
- [11] Young WB, Silberstein SD. Occipital nerve stimulation for primary headaches. *J Neurosurg Sci* 2012;56:307–12.
- [12] Stilling JM, Monchi O, Amoozegar F, Debert CT. Transcranial magnetic and direct current stimulation (TMS/tDCS) for the treatment of headache: a systematic review. *Headache* 2019;59:339–57. <https://doi.org/10.1111/head.13479>.
- [13] Moisset X, Pereira B, Ciampi de Andrade D, Fontaine D, Lantéri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. *J Headache Pain* 2020;21:142. <https://doi.org/10.1186/s10194-020-01204-4>.
- [14] Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. *Lancet Neurol* 2012;11:708–19. [https://doi.org/10.1016/S1474-4422\(12\)70139-4](https://doi.org/10.1016/S1474-4422(12)70139-4).
- [15] Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, de Tommaso M, et al. Neuromodulation of chronic headaches: position statement from the European headache federation. *Headache Pain* 2013;14:86. <https://doi.org/10.1186/1129-2377-14-86>.
- [16] Evers S. Non-invasive neurostimulation methods for acute and preventive migraine treatment – a narrative review. *J Clin Med* 2021;10:3302. <https://doi.org/10.3390/jcm10153302>.
- [17] Demarquay G, Mawet J, Guégan-Massardier E, de Gaalon S, Donnet A, Giraud P, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 3: non-pharmacological treatment. *Rev Neurol (Paris)* 2021;177:753–9. <https://doi.org/10.1016/j.neurol.2021.07.009>.
- [18] Lefaucheur JP. Cortical neurostimulation for neuropathic pain: state of the art and perspectives. *Pain* 2016;157(Suppl 1):S81–9. <https://doi.org/10.1097/j.pain.0000000000000401>.
- [19] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017;128:56–92. <https://doi.org/10.1016/j.clinph.2016.10.087>.
- [20] Pinto CB, Teixeira Costa B, Duarte D, Fregni F. Transcranial direct current stimulation as a therapeutic tool for chronic pain. *J ECT* 2018;34:e36–50. <https://doi.org/10.1097/YCT.0000000000000518>.
- [21] Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. *Int J Neuropsychopharmacol* 2021;24:256–313. <https://doi.org/10.1093/ijnp/pyaa051>.
- [22] Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum* 2006;54:3988–98. <https://doi.org/10.1002/art.22195>.
- [23] Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 2006;122:197–209. <https://doi.org/10.1016/j.pain.2006.02.023>.
- [24] Mori F, Codeca C, Kusayanagi H, Montealeone F, Buttari F, Fiore S, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *J Pain* 2010;11:436–42. <https://doi.org/10.1016/j.jpain.2009.08.011>.
- [25] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2018;3:CD008208. <https://doi.org/10.1002/14651858.CD008208.pub4>.
- [26] Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol* 2016;23:1489–99. <https://doi.org/10.1111/ene.13103>.
- [27] Lefaucheur JP, Wendling F. Mechanisms of action of tDCS: a brief and practical overview. *Neurophysiol Clin* 2019;49:269–75. <https://doi.org/10.1016/j.neucli.2019.07.013>.
- [28] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527:633–9. <https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x>.
- [29] Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J Physiol* 2013;591:2563–78. <https://doi.org/10.1113/jphysiol.2012.247171>.
- [30] Medeiros LF, de Souza IC, Vidor LP, de Souza A, Deitos A, Volz MS, et al. Neurobiological effects of transcranial direct current stimulation: a review. *Front Psychiatr* 2012;3:110. <https://doi.org/10.3389/fpsy.2012.00110>.
- [31] Choi C-H, Iordanishvili E, Shah NJ, Binkofski F. Magnetic resonance spectroscopy with transcranial direct current stimulation to explore the underlying biochemical and physiological mechanism of the human brain: a systematic review. *Hum Brain Mapp* 2021;42:2642–71. <https://doi.org/10.1002/hbm.25388>.
- [32] Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol* 2003;553:293–301. <https://doi.org/10.1113/jphysiol.2003.049916>.
- [33] Siniatchkin M, Sendacki M, Moeller F, Wolff S, Jansen O, Siebner H, et al. Abnormal changes of synaptic excitability in migraine with aura. *Cerebr Cortex* 2012;22:2207–16. <https://doi.org/10.1093/cercor/bhr248>.
- [34] Feng Y, Zhang B, Zhang J, Yin Y. Effects of non-invasive brain stimulation on headache intensity and frequency of headache attacks in patients with migraine: a systematic review and meta-analysis. *Headache* 2019;59:1436–47. <https://doi.org/10.1111/head.13645>.
- [35] Cai G, Xia Z, Leigh C, Xiao F, Datta A, Androurakis XM. A systematic review and meta-analysis on the efficacy of repeated transcranial direct current stimulation for migraine. *J Pain Res* 2021;14:1171–83. <https://doi.org/10.2147/JPR.S295704>.
- [36] Ayache SS, Chalah MA. Transcranial direct current stimulation and migraine – the beginning of a long journey. *J Clin Med* 2020;9:1194. <https://doi.org/10.3390/jcm9041194>.
- [37] Andrade SM, de Brito Aranha REL, de Oliveira EA, de Mendonça CTPL, Martins WKN, Alves NT, et al. Transcranial direct current stimulation over the primary motor vs prefrontal cortex in refractory chronic migraine: a pilot randomized controlled trial. *J Neurol Sci* 2017;378:225–32. <https://doi.org/10.1016/j.jns.2017.05.007>.
- [38] Dalla Volta G, Marceglia S, Zavarise P, Antonaci F. Cathodal tDCS guided by thermography as adjunctive therapy in chronic migraine patients: a sham-controlled pilot study. *Front Neurol* 2020;11:121. <https://doi.org/10.3389/fneur.2020.00121>.
- [39] Cerrahoğlu Şirin T, Aksu S, Hasirci Bayir BR, Ulukan Ç, Karamürsel S, Kurt A, et al. Is allodynia a determinant factor in the effectiveness of transcranial direct current stimulation in the prophylaxis of migraine? *Neuromodulation* 2021;24:899–909. <https://doi.org/10.1111/ner.13409>.
- [40] Rahimi MD, Fadardi JS, Saedi M, Bigdeli I, Kashiri R. Effectiveness of cathodal tDCS of the primary motor or sensory cortex in migraine: a randomized

- controlled trial. *Brain Stimul* 2020;13:675–82. <https://doi.org/10.1016/j.brs.2020.02.012>.
- [41] Silberstein S, Tfelt-Hansen P, Dodick DW, Limmroth V, Lipton RB, Pascual J, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia* 2008;28:484–95. <https://doi.org/10.1111/j.1468-2982.2008.01555.x>.
- [42] Sacco S, Braschinsky M, Ducros A, Lampl C, Little P, van den Brink AM, et al. European headache federation consensus on the definition of resistant and refractory migraine: developed with the endorsement of the European Migraine & Headache Alliance (EMHA). *J Headache Pain* 2020;21:76. <https://doi.org/10.1186/s10194-020-01130-5>.
- [43] Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* 2006;117:845–50. <https://doi.org/10.1016/j.clinph.2005.12.003>.
- [44] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol* 2016;127:1031–48. <https://doi.org/10.1016/j.clinph.2015.11.012>.
- [45] Kosinski M, Bayliss MS, Bjorner JB, Ware JR, Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12:963–74. <https://doi.org/10.1023/a:1026119331193>.
- [46] Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache-related disability. *Neurology* 2001;56:S20–8. https://doi.org/10.1212/wnl.56.suppl_1.s20.
- [47] Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33. <https://doi.org/10.1097/00005650-199603000-00003>.
- [48] Zigmund AS, Snaith RT. The hospital anxiety depression scale. *Acta Psycho Scand* 1983;67:361–70. <https://doi.org/10.1111/j.1600-0447.1983.tb09716.x>.
- [49] Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry* 2007;4:28–37.
- [50] Smelt AF, Assendelft WJ, Terwee CB, Ferrari MD, Blom JW. What is a clinically relevant change on the HIT-6 questionnaire? An estimation in a primary-care population of migraine patients. *Cephalalgia* 2014;34:29–36. <https://doi.org/10.1177/0333102413497599>.
- [51] Lipton R, Desai P, Sapra S, Buse D, Fanning K, Reed M. How much change in headache-related disability is clinically meaningful? Estimating minimally important difference (MID) or change in MIDAS using data from the AMPP study. *Headache J Head Face Pain* 2017;57:165.
- [52] Linde K, Streng A, Jürgens A, Hoppe A, Brinkhaus B, Witt C, et al. Acupuncture for patients with migraine: a randomized controlled trial. *JAMA* 2005;293:2118–25. <https://doi.org/10.1001/jama.293.17.2118>.
- [53] Tfelt-Hansen P, Pascual J, Ramadan N, Dahlöf C, D'Amico D, Diener HC, et al. International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia* 2012;32:6–38. <https://doi.org/10.1177/0333102411417901>.
- [54] Salim A, Mackinnon A, Christensen H, Griffiths K. Comparison of data analysis strategies for intent-to-treat analysis in pre-test-post-test designs with substantial dropout rates. *Psychiatr Res* 2008;160:335–45. <https://doi.org/10.1016/j.psychres.2007.08.005>.
- [55] Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, et al. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain* 2011;152:1478–85. <https://doi.org/10.1016/j.pain.2011.01.034>.
- [56] Hodaj H, Alibeu JP, Payen JF, Lefaucheur JP. Treatment of chronic facial pain including cluster headache by repetitive transcranial magnetic stimulation of the motor cortex with maintenance sessions: a naturalistic study. *Brain Stimul* 2015;8:801–7. <https://doi.org/10.1016/j.brs.2015.01.416>.
- [57] Hodaj H, Payen JF, Hodaj E, Dumolard A, Maindet C, Cracowski JL, et al. Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex. *Clin Neurophysiol* 2020;131:1423–32. <https://doi.org/10.1016/j.clinph.2020.03.022>.
- [58] Agostoni EC, Barbanti P, Calabresi P, Colombo B, Cortelli P, Frediani F, et al. Italian chronic migraine group. Current and emerging evidence-based treatment options in chronic migraine: a narrative review. *J Headache Pain* 2019;20:92. <https://doi.org/10.1186/s10194-019-1038-4>.
- [59] Ducros A, de Gaalon S, Roos C, Donnet A, Giraud P, Guégan-Massardier E, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: pharmacological treatment. *Rev Neurol (Paris)* 2021;177:734–52. <https://doi.org/10.1016/j.neuro.2021.07.006>.
- [60] Gribbin CL, Dani KA, Tyagi A. Chronic migraine: an update on diagnosis and management. *Neurol India* 2021;69:S67–75. <https://doi.org/10.4103/0028-3886.315972>.
- [61] Urits I, Gress K, Charipova K, Zamarripa AM, Patel PM, Lassiter G, et al. Pharmacological options for the treatment of chronic migraine pain. *Best Pract Res Clin Anaesthesiol* 2020;34:383–407. <https://doi.org/10.1016/j.bpa.2020.08.002>.
- [62] Frank F, Ulmer H, Sidoroff V, Broessner G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: a systematic review and meta-analysis. *Cephalalgia* 2021;41:1222–39. <https://doi.org/10.1177/03331024211018137>.
- [63] Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007;47:170–80. <https://doi.org/10.1111/j.1526-4610.2006.00684.x>.
- [64] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–21. <https://doi.org/10.1016/j.jpain.2007.09.005>.
- [65] Silberstein S, Lipton R, Dodick D, Freitag F, Mathew N, Brandes J, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache* 2009;49:1153–62. <https://doi.org/10.1111/j.1526-4610.2009.01508.x>.
- [66] Han L, Liu Y, Xiong H, Hong P. CGRP monoclonal antibody for preventive treatment of chronic migraine: an update of meta-analysis. *Brain Behav* 2019;9:e01215. <https://doi.org/10.1002/brb3.1215>.
- [67] Rothrock JF, Adams AM, Lipton RB, Silberstein SD, Jo E, Zhao X, et al. FORWARD study: evaluating the comparative effectiveness of OnabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. *Headache* 2019;59:1700–13. <https://doi.org/10.1111/head.13653>.
- [68] Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu M, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study. *J Headache Pain* 2021;22:113. <https://doi.org/10.1186/s10194-021-01322-7>.
- [69] Ray J, Hutton E, Matharu M. OnabotulinumtoxinA in migraine: a review of the literature and factors associated with efficacy. *J Clin Med* 2021;10:2898. <https://doi.org/10.3390/jcm10132898>.
- [70] Antal A, Kriener N, Lang N, Boros K, Paulus W. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. *Cephalalgia* 2011;31:820–8. <https://doi.org/10.1177/0333102411399349>.
- [71] Rocha S, Melo L, Boudoux C, Foerster Á, Araújo D, Monte-Silva K. Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: a pilot randomized controlled trial. *J Neurol Sci* 2015;349:33–9. <https://doi.org/10.1016/j.jns.2014.12.018>.
- [72] Wickmann F, Stephani C, Czesnik D, Klinker F, Timäus C, Chaieb L, et al. Prophylactic treatment in menstrual migraine: a proof-of-concept study. *J Neurol Sci* 2015;354:103–9. <https://doi.org/10.1016/j.jns.2015.05.009>.
- [73] Ahdab R, Mansour AG, Khazen G, El-Khoury C, Sabbouh TM, Salem M, et al. Cathodal transcranial direct current stimulation of the occipital cortex in episodic migraine: a randomized sham-controlled crossover study. *J Clin Med* 2019;9:60. <https://doi.org/10.3390/jcm9010060>.
- [74] Mansour AG, Ahdab R, Khazen G, El-Khoury C, Sabbouh TM, Salem M, et al. Transcranial direct current stimulation of the occipital cortex in medication overuse headache: a pilot randomized controlled cross-over study. *J Clin Med* 2020;9:1075. <https://doi.org/10.3390/jcm9041075>.
- [75] Pohl H, Moisa M, Jung HH, Brenner K, Aschmann J, Riederer F, et al. Long-term effects of self-administered transcranial direct current stimulation in episodic migraine prevention: results of a randomized controlled trial. *Neuromodulation* 2021;24:890–8. <https://doi.org/10.1111/ner.13292>.
- [76] Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, et al. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. *J Med Assoc Thai* 2012;95:1003–12.
- [77] De Icco R, Putortì A, De Paoli I, Ferrara E, Cremascoli R, Terzaghi M, et al. Anodal transcranial direct current stimulation in chronic migraine and medication overuse headache: a pilot double-blind randomized sham controlled trial. *Clin Neurophysiol* 2021;132:126–36. <https://doi.org/10.1016/j.clinph.2020.10.014>.
- [78] Grazi L, Usai S, Bolognini N, Grignani E, Sansone E, Tramacere I, et al. No efficacy of transcranial direct current stimulation on chronic migraine with medication overuse: a double blind, randomised clinical trial. *Cephalalgia* 2020;40:1202–11. <https://doi.org/10.1177/0333102420931050>.
- [79] Monte-Silva K, Kuo M-F, Hesselthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul* 2013;6:424–32. <https://doi.org/10.1016/j.brs.2012.04.011>.
- [80] Hodkinson DJ, Veggeberg R, Wilcox SL, Scriveri S, Burstein R, Becerra L, et al. Primary somatosensory cortices contain altered patterns of regional cerebral blood flow in the interictal phase of migraine. *PLoS One* 2015;10:e0137971. <https://doi.org/10.1371/journal.pone.0137971>.
- [81] Moisset X, Lefaucheur JP. Non pharmacological treatment for neuropathic pain: invasive and non-invasive cortical stimulation. *Rev Neurol (Paris)* 2019;175:51–8. <https://doi.org/10.1016/j.neuro.2018.09.014>.
- [82] Henssen D, Giesen E, van der Heiden M, Kerperien M, Lange S, van Cappellen van Walsum AM, et al. A systematic review of the proposed mechanisms underpinning pain relief by primary motor cortex stimulation in animals. *Neurosci Lett* 2020;719:134489. <https://doi.org/10.1016/j.neulet.2019.134489>.
- [83] Gamal-Eltrabily M, Martínez-Lorenzana G, González-Hernández A, Condés-Lara M. Cortical modulation of nociception. *Neuroscience* 2021;458:256–70. <https://doi.org/10.1016/j.neuroscience.2021.01.001>.
- [84] Ahdab R, Ayache SS, Brugières P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression.

- Neurophysiol Clin 2010;40:27–36. <https://doi.org/10.1016/j.neucli.2010.01.001>.
- [85] Amadi U, Allman C, Johansen-Berg H, Stagg CJ. The homeostatic interaction between anodal transcranial direct current stimulation and motor learning in humans is related to GABAA activity. *Brain Stimul* 2015;8:898–905. <https://doi.org/10.1016/j.brs.2015.04.010>.
- [86] Cosentino G, Brighina F, Talamanca S, Paladino P, Vigneri S, Baschi R, et al. Reduced threshold for inhibitory homeostatic responses in migraine motor cortex? A tDCS/TMS study. *Headache* 2014;54:663–74. <https://doi.org/10.1111/head.12249>.
- [87] Fischer DB, Fried PJ, Ruffini G, Ripolles O, Salvador R, Banus J, et al. Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex. *Neuroimage* 2017;157:34–44. <https://doi.org/10.1016/j.neuroimage.2017.05.060>.
- [88] Chen C, Fang Y, Wang X, Bao SC, Tang Z, Tong RK. Excitation comparison between multi-site stimulation using network-based tDCS and focal stimulation using high-definition tDCS. *Annu Int Conf IEEE Eng Med Biol Soc* 2019: 6884–7. <https://doi.org/10.1109/EMBC.2019.8857287>. 2019.
- [89] de Almeida Rodrigues ET, da Silva Machado DG, Leon de Mendonça CTP, da Rocha Souto C, Ries A, Torro N, et al. Multisite transcranial direct current stimulation in two patients with Alzheimer's disease: a 10-month follow-up study. *Neurophysiol Clin* 2020;50:393–5. <https://doi.org/10.1016/j.neucli.2020.08.001>.
- [90] Brigo F, Storti M, Tezzon F, Manganotti P, Nardone R. Primary visual cortex excitability in migraine: a systematic review with meta-analysis. *Neurol Sci* 2013;34:819–30. <https://doi.org/10.1007/s10072-012-1274-8>.
- [91] Coppola G, Di Lorenzo C, Parisi V, Lisicki M, Serrao M, Pierelli F. Clinical neurophysiology of migraine with aura. *J Headache Pain* 2019;20:42. <https://doi.org/10.1186/s10194-019-0997-9>.
- [92] Karabanov A, Ziemann U, Hamada M, George MS, Quartarone A, Classen J, et al. Consensus paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. *Brain Stimul* 2015;8:993–1006. <https://doi.org/10.1016/j.brs.2015.06.017>.
- [93] Wittkopf PG, Larsen DB, Graven-Nielsen T. Protocols for inducing homeostatic plasticity reflected in the corticospinal excitability in healthy human participants: a systematic review and meta-analysis. *Eur J Neurosci* 2021;54: 5444–61. <https://doi.org/10.1111/ejn.15389>.
- [94] Lendvai IS, Maier A, Scheele D, Hurlmann R, Kinfe TM. Spotlight on cervical vagus nerve stimulation for the treatment of primary headache disorders: a review. *J Pain Res* 2018;11:1613–25. <https://doi.org/10.2147/JPR.S129202>.
- [95] Riggs A, Patel V, Paneri B, Portenoy RK, Bikson M, Knotkova H. At-home Transcranial Direct Current Stimulation (tDCS) with telehealth support for symptom control in chronically-ill patients with multiple symptoms. *Front Behav Neurosci* 2018;12:93. <https://doi.org/10.3389/fnbeh.2018.00093>.