Low intensity, transcranial, alternating current stimulation reduces migraine attack burden in a home application set-up

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Running title: 'inhibitory' tACS over the visual cortex reduces migraine attack burden

Category: Original article

Funding Sources: This study (AA, WP) was supported by the Migraine Research Foundation (NY).

Disclosures: The authors have no conflicts of interest related to the content of this study. WP is a member of the scientific advisory board of EBS technologies and Precisis AG.

Registered in the German Register for Clinical Studies (DRKS00011878)

Keywords: tACS, migraine, acute-treatment, visual cortex, transcranial stimulation.

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Highlights:

- Low intensity, high frequency tACS applied over the visual cortex in the early phase of a migraine attack reduces pain burden
- Low intensity, high frequency tACS over the motor cortex decreases the amplitude of motor evoked potentials
- Home-use is associated with technical challenges leading to compliance problems and a high drop-out rate

Abstract

Objective: Low intensity, high frequency transcranial alternating current stimulation (tACS) over the visual cortex was investigated in 40 patients as a home therapy option in the acute management of migraine.

Methods: This double-blind, placebo-controlled parallel group study assigned the migraine patients to receive either active or sham stimulation with the number of terminated attacks two hours post-stimulation as the primary endpoint. We used 0.4 mA, 140 Hz stimulation for 15 min to treat a maximum of five migraine attacks at home over the course of six weeks.

Results: Twenty-five patients completed the study, 16 in the active and 9 in the sham group with a total of 102 treated migraine attacks. The percentage of terminated migraine attacks not requiring acute rescue medication was significantly higher in the active (21.5 %) than in the sham group (0%), and the perceived pain after active stimulation was significantly less for 1-4 hours post stimulation than after sham stimulation.

Interpretation: tACS over the visual cortex has the potential to terminate migraine attacks. The high drop-out rate due to compliance problems suggests that this method is impeded by its complexity and time consuming setup.

Introduction

Transcranial magnetic (TMS) and direct current stimulation (tDCS) have shown efficacy in the acute and prophylactic treatment of migraine in placebo-controlled studies [1-10]. The application of two-pulses of TMS over the visual cortex or over the painful area has been claimed to ameliorate or terminate migraine pain [3, 5]. This effect is assumed to be based on influencing neuronal activity and, in the case of an aura, interfering with the occurrence of cortical spreading depression in the early phase of the migraine attack [11].

In healthy subjects transcranial alternating current stimulation (tACS) with 0.4 mA at 140 Hz applied over the primary motor cortex (M1) can significantly decrease the amplitude of motor evoked potentials (MEPs) at rest [12]. In the present study we aimed to target the visual cortex of migraine patients at the onset of the migraine attack by having the patient apply tACS at home. We hypothesized that modifying cortical activity through the application of high-frequency transcranial oscillations might adjust behaviorally 'maladaptive' brain states and induce a new balance, forcing the network to restore adequate synchronization and excitation.

Transcranial stimulation, including tACS is normally administered by medical professionals in a clinical setting to ensure correct administration of the treatment. The necessity to visit the hospital immediately to treat a migraine attack makes this type of treatment unpractical. The necessity of repeated visits may also increase drop-out rates in long-term studies e.g. in depression [13], or even interfere with patient-recruitment. Self-administration of tACS by the patients would counteract this disadvantage. The feasibility of this approach has been demonstrated for trigeminal neuralgia and menstrual migraine [14], [10].

The present study aimed at promoting a safe and feasible protocol for self-administered tACS in the home therapy of migraine attacks. Special attention was paid to optimal user training for a maximally standardized and reproducible transcranial stimulation setup.

Methods

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

Patients

Forty migraine patients were recruited for the study. Inclusion criteria were: migraine with or without aura and disease duration ≥ 6 months (Headache Classification Committee of the International Headache Society, 2004). Exclusion criteria were: significant chronic health disorders, diagnosed neuropsychiatric disorders, pregnancy or breast feeding, history of substance abuse or dependence, a history of neurological disorders other than migraine, an implanted pacemaker and cranial metallic hardware. All patients were naïve to transcranial stimulation and none took prophylactic migraine medication during the study period. If applicable, female patients were advised to continue contraception (that was started at least 6 month prior to enrollment into the study) during the whole study period. None of the patients had a history of acute migraine medication overuse.

Table 1. *Demographics and medical history of the patients*

	tACS (n=16)	**Sham (n=9)**
With aura	9	5
Without aura	7	4
Mean age (SD)	31.1 (8.9)	28.1 (10.5)

Mean duration in years (SD)	13.7 (7.8)	14.8 (10.3)
Mean number of attacks/year (SD)	28.7 (18.5)	42.8 (42.2)
Pain localization		
unilateral	11	5
bilateral	5	4
with Family history	9	7
Medication		
ASS	2	1
Triptans	4	3
Ibuprofen	2	1
Paracetamol	4	3
Others *-Antidepressants* *-Metamizole* *-Thyroid Hormone*	 2 1 1	 0 0 0
Oral contraception	9	5
Nicotin	4	1

Experimental design

The primary endpoint of this double-blind, placebo-controlled study was the termination of the migraine attacks within two hours post stimulation. Patients were asked to maintain a headache diary throughout the study duration. During the study the frequency of the migraine attacks was recorded, including onset and duration of the pain, number of migraine-related days and the type of analgesics taken. Patients were advised to document the degree of pain on a numerical analogue scale (NAS) with severity ratings ranging from 0 to 10 at onset of a migraine attack as well as 1 hour and 2, 4, 8, 24, and 48 hours thereafter.

Transcranial alternating current stimulation

The patients were assigned to receive either treatment ‘A’ or ‘B’, according to a computer randomization list. The battery-driven, constant current stimulators (NeuroConn, Ilmenau, Germany) were coded by the coordinating investigator, who had no contact with the patients. The stimulation was then applied by the patient at home.

Since electrode preparation and positioning are essential factors in reproducible remotely-supervised treatment [15], the patients were given detailed instructions and a training session in the department before being allowed to use the stimulator. Unknown to the patients, the parameters used during the home stimulation sessions, including the time and duration of the sessions were stored in the stimulator.

Saline-soaked sponge electrodes were used. The stimulating electrode (4 x 4 cm) was placed over the Oz and the return electrode (5 x 7 cm) over the Cz electrode positions. According to a modeling study these electrode positions give current densities in the range of 0.05–0.15 A/m^2, the higher intensities being allocated to the medial, as compared to the lateral occipital cortex [16]. tACS with 0.4 mA was applied for 15 min, including 20 sec ramp-up and ramp-down phases. For sham stimulation, the electrodes were placed in the same positions as for active stimulation, but the stimulator was turned off automatically after 30 s of stimulation. Both the patients and the training investigator were blinded with regard to the type of tACS applied. The patients were instructed to start the stimulation session at the beginning of the migraine attack (e.g. after the appearance of aura or pain). The patients were aware of the fact that they would receive either sham or real stimulation.

Since any potential adverse effects of this technique in a patient population are not yet known, the patients completed a questionnaire after the whole stimulation session. It contained rating scales for the presence of discomforting sensations like pain, tingling, itching or burning under the electrodes due to tACS [17] (1 = very mild and 5 = extremely strong intensity).

Statistical analysis

Chi-squared test was used to compare the number of terminated attacks (with and without medication) in the active and sham groups. With regard to the primary endpoint a *p*-value of ≤ 0.05 was considered significant. Repeated measures ANOVA was used to test for differences in pain perception with the factors 'type of stimulation' (active and sham) and 'time' (before and after treatment, hours). All other analyses are considered exploratory and confidence intervals as well as p-values are reported without correction for multiple testing.

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 NAS from one to five, one being very mild and five being of an extremely strong intensity of any given side-effect.

Results

Forty patients were randomized using a computer algorithm to get real (25 patients) or sham (15 patients) stimulation. Fifteen patients, nine from the active and six from the sham group, had to be excluded from evaluation during the course of the study. Eight were excluded because they failed to perform any stimulation. Four of these were only detected by analyzing the stimulator memory. Four patients had no migraine attacks during the study period, two patients decided to withdraw without giving any reason and one patient experienced a panic attack before the stimulation. Twenty-five patients returned a valid migraine diary, the demographical characteristics and medical history of which is summarized in Table 1. These 25 patients suffered a total of 102 documented migraine attacks during the study.

A total of 65 migraine attacks were treated in the active group and, 37 in the sham group. In the active group 27 attacks were treated with drugs within two hours after the stimulation compared to 14 in the sham group (42% vs. 39%). In the attacks

without pharmacological interventions the pain abated within two hours post-stimulation in 14 of the 38 attacks in the active group, but in none of the 23 attacks in the sham group ($p < 0.001$). Furthermore, in these attacks, pain severity after stimulation was significantly lower after tACS than after sham stimulation in the first four hours (main effect: $F(1,59)=13,307$, $p<0.0005$; interaction: $F(7,413)=5.065$ $p<0.00002$) (Fig.1).

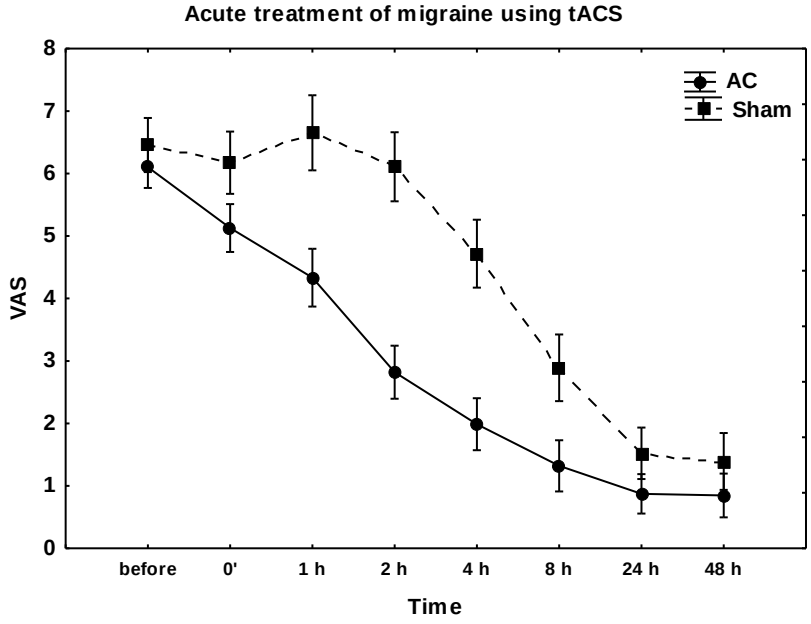

Fig.1. Effect of 140 Hz 0.4 mA tACS applied over the visual cortex on pain severity during migraine attack. Bars represent SDs.

Adverse effects of tACS: No medical interventions other than acute migraine medications were required; 23 patients completed the questionnaire, 15 in the active and 8 in the sham group. Table 2 summarizes the adverse effects due to stimulation.

Table 2: *Adverse effects of tACS reported after stimulation. N: number of patients;* MI = mean intensity (1 = very mild and 5 = extremely strong intensity)

	Pain under the electrodes		**Tingling**		**Itching**	
	N	MI	N	MI	N	MI

tACS (n=16)	1	2	5	1.8	5	1.4
Sham (n=9)	1	3	4	1.8	2	1.3
	Nervousness		**Fatigue**		**Unpleasantness**	
	N	MI	N	MI	N	MI
tACS (n=?)	1	4.0	6	2.2	2	2.0
Sham (n=?)	3	2.5	6	2.2	5	3.3

Discussion

Our hypothesis that inhibitory tACS over the visual cortex could be an effective acute treatment option was based on data suggesting that migraine is associated with higher neuronal excitability or responsiveness (e.g. [18-24]) and the observation that 0.4 mA 140 Hz tACS over the motor cortex probably decreases cortical excitability [12]. Accordingly we found that a significantly higher percentage of migraine attacks were terminated within two hours post stimulation in the tACS group,. Nevertheless, only less than one in four of the attacks could be completely terminated by this intervention; in almost half of the attacks additional acute medication was required. In the sham group 38% of the attacks were treated with drugs and none of them responded to the sham stimulation.

Despite the variety of pharmaceutical options available for the prophylaxis or acute treatment of migraine, a substantial proportion of patients remains resistant to drug therapy. Several non-pharmaceutical alternatives, such as exercise and acupuncture, have been compared with common prophylactic medications [25-27] and seem to offer some benefit for migraine patients [28]. In a similar approach, two pulses of TMS at low or high intensity were applied in an open-label study during acute migraine attacks. Stimulation was over the region of pain in patients without aura, or over the visual cortex in patients with aura [5]. Pain intensity was reduced by 75% up to 20

minutes post-TMS. 32% of patients reported no further headache for up to 24 hours after one treatment, 29% after two treatments and 40% after three sessions. In another study, 164 patients with aura were stimulated over the visual cortex within one hour of aura onset using a randomized, double-blind, parallel-group, sham-controlled design [3]. Up to three attacks were treated over a three-month period. Real TMS was more effective than sham stimulation in alleviating pain at two hours (39% vs. 22%), and for sustained pain relief at 24 hours (29% vs. 16%) and 48 hours (27% vs. 13%). Based on telephone interviews single pulse TMS in 190 episodic or chronic migraine patients reduced the number of headache days after 12 weeks of treatment in nearly 60% of patients in whom acute medications were contraindicated or ineffective[29]. Nevertheless, the discontinuation rate was 55% in this study. Repetitive TMS (rTMS) as a preventative treatment both for episodic and chronic migraine resulted in mixed outcomes [4, 30, 31]. So far, the efficacy of prophylactic anodal and cathodal tDCS as well as rTMS has been mainly tested in open label studies with diverse results [1, 6, 10, 32, 33].

To our knowledge, tACS has never been employed before in patients with migraine. Previous data suggest that stimulating the motor cortex of healthy young subjects with 140 Hz tACS at 0.4 mA can decrease the amplitude of MEPs [12] for more than one hour after stimulation. Using lower frequencies in the alpha range and higher intensities, tACS induced increased alpha power [34, 35]. We assume that tACS over the visual cortex may not only reduce local excitability but possibly modify the activity of the brainstem through nociceptive pathways [36]. It is suggested that there is a functional connection between the visual cortex and brainstem second-order nociceptors in the spinal trigeminal nucleus. Therefore, inhibiting the projection from the visual cortex to the brainstem might result in less pain during attacks.

Home therapy was well tolerated by all patients. The majority of user feedback after stimulation concerning the efficacy was either positive or neutral. Nevertheless, the main reason for the substantial fraction of non-compliance might be the time consuming task of positioning the electrodes before stimulation as compared to taking a pill. In future studies, family members should be involved in the training sessions, when stimulation is to be performed at home as an acute intervention. Besides this, although the patients were instructed to start the stimulation immediately after the first signs of the migraine attack appeared, many of them probably did not do that because the baseline VAS values were relatively high. Furthermore, due to the high drop-out rate, the current study is limited by the small remaining sample size.

In summary, acute application of tACS over the visual cortex (0,4 mA, 140 Hz) for 15 minutes was able to terminate migraine attacks. Despite home treatment the logistic effort was high with strict training and supervision by healthcare professionals. Improved strategies to further simplify the procedure will certainly reduce the drop-out rate. Fine tuning of dose titration may also increase efficacy. Also strategies to increase efficacy in combination with neuroplasticity modifying or with migraine prophylactic drugs warrant further investigations.

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