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Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: A pilot randomized controlled trial

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ABSTRACT

Purpose: The aims of this paper are (i) to compare the excitability of visual cortex in migraine patients with healthy volunteers; and (ii) if an abnormal excitability has been found, to modulate cortical excitability in migraine patients with transcranial direct current stimulation (tDCS) and observe their clinical and neurophysiological effects.
Methods: The study was divided into two steps. A cross-sectional study (step 1) was conducted to compare the cortical excitability of 23 migraineurs (11 with and 12 without aura) on 11 healthy individuals. On step 2, a randomized, double blinded, controlled pilot trial was carried on with 19 migraineurs, randomly divided into: experimental and control group. During 12 sessions, experimental and group received active tDCS to visual cortex and control group received sham tDCS. The headache diary was applied for a total of 90 days (before, during and after tDCS sessions). Phosphene threshold (PT) induced by transcranial magnetic stimulation was recorded to measure the excitability of the visual cortex before and after each session.
Results: Step 1 showed higher level of cortical excitability between migraineurs when compared to healthy volunteers; therefore, cathodal tDCS was applied over visual cortex in step 2. After tDCS application, a significant decrease was observed in a number of migraine attacks, painkiller intake and duration of each attack just in experimental group. The analysis of PT indicated no difference in cortical excitability after tDCS.
Conclusions: Findings of the study suggested that inhibitory tDCS on visual cortex might be an alternative and non-pharmacological treatment for migraine prophylaxis. However the clinical improvements of patients after tDCS treatment are not correlated with changes in cortical excitability.

1. Introduction

Migraine is a chronic, multifactorial and neurovascular disease manifested by recurrent attacks of headaches that promote disability and dysfunction of the autonomic nervous system [1]. The identification of preventive treatment that effectively controls this common neurovascular disorder has been very difficult since the pathophysiological mechanisms for migraine are still not entirely elucidated [2]. It is widely accepted that abnormal excitability of occipital cortex appears to play a pivotal role in migraine pathophysiology. Therefore, it has been proposed that excitability level of visual cortex neurons in migraine can drive appropriate therapeutic approaches [3].

Recently, non-invasive brain stimulation has been used to induce durable changes in cortical excitability and potentially correct the neural activity abnormalities found in migraine patients. However, as it is not clear whether the symptoms of migraine result on a hyper- [4,5] or a hypoexcitability of the visual cortex [6–8] different stimulation paradigms have been applied depending on the author's hypothesis whether the migraine brain is hyper- or hypoexcitable. For instance, in order to decrease or prevent symptoms of the disease, some authors applied inhibitory stimulations over the visual cortex to correct an eventual cortical hyperexcitability [9,10]. In contrast, excitatory stimulation to increase a supposed abnormal hypoexcitability is also used [3,8]. Therefore, the lack of positive outcomes resulting from brain stimulation, as seen by Conforto et al. [11], could eventually be due to an incorrect baseline excitability assumption.

We performed a 2-step trial: on the first step we compared the interictal excitability of the visual cortex in migraine patients, with and without aura, on healthy subjects. On the second step, we modulated the impaired interictal excitability in migraineurs according to first-step findings and observed its clinical implications. To study cortical

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excitability, the phosphene threshold (PT), a representative of visual cortex excitability induced by transcranial magnetic stimulation (TMS), was analyzed. PT is defined as the lowest intensity of a TMS pulse required to evoke phosphenes [12]. Studies using TMS have found significantly lower PT and a much higher proportion to evoke phosphenes in migraineurs compared with healthy volunteers, which benefits the cortical hyperexcitability theory [4,13]. Other studies have achieved the opposite result [6,8] pointing out to decreased interictal cortical excitability in migraineurs. To modulate the abnormal interictal excitability in migraine patients, transcranial direct current stimulation (tDCS) was applied. TDCS results in motor cortical excitability changes in humans that occur during the application of direct current and remain stable for up to 1 h after stimulation. Anodal tDCS increases excitability, while cathodal tDCS decreases it [14–16]. Some studies have demonstrated the effectiveness of using anodal [3] and cathodal tDCS [9] for migraine treatment.

2. Methods

2.1. Subjects

Twenty-three subjects diagnosed with migraine, 11 with (MA; 26 ± 9 years; 8 female) and 12 without aura (MwoA, 24 ± 6 years; 11 female), were compared to eleven healthy volunteers (HV; 22 ± 2 years; 9 female) who had no family and personal history of migraine. Patients and healthy volunteers were recruited via advertisements on the university website and local newspaper between July 2012 and September 2013. Inclusion criteria for migraine patients were: (i) migraine diagnosis according to the International Classification of Headache Disorders (ICHD-II) criteria [17] by a physician; and (ii) no use of prophylactic medications within six months prior to study initiation. For control subjects, inclusion criteria were: not presenting a headache crisis in the last 12 months assessed according to IHCD-II criteria. All participants were ages ranged from 18 to 50 years old and were not taking any drugs that could influence cortical excitability or other regular medication. Subjects who had any contraindication to TMS [18] were excluded. The same safety criteria were applied for tDCS (experiment 2).

Experiments were conducted under a protocol approved by local Research Ethics Committee and were performed according to the Declaration of Helsinki. All participants gave their written informed consent prior to the experiment.

2.2. Experimental design

The study consists of two experiments with different methodological characteristics. The therapeutic study was registered with www.clinicalTrials.gov (NCT01886274).

2.2.1. Experiment 1 (electrophysiological study)

The experiment 1 was conducted in a cross-sectional study design from July 2012 to January 2013. To perform PT measure, in a semi-darkened room, volunteers were instructed to sit comfortably in a shiatsu chair and use a blindfold. A 10 cm circular coil connected to stimulator (Neurosoft, Russia; peak magnetic field = 2.2 T) was placed in a vertical position (its handle pointing upward) on the inion–nasion line, with its inferior limit 1 cm above the inion, as described before [19]. The circular coil may induce a larger electric field increasing chances of evoking phosphenes [20]. After each TMS single-pulse over visual cortex, the volunteers were encouraged to relate any sensory experiences (e.g. visual, smell or taste sensations). The coil position was defined as the site where stimulation resulted consistently in phosphenes (short-lasting flashes or lines in the subject's visual field). Then, the stimulator intensity (initially applied at 60% of stimulator output) was adjusted until the subject reported phosphenes at least five out of ten trials (phosphene threshold) and was expressed as a percentage of maximum stimulator output. To determine interictal excitability of visual cortex in migraine patients, we used two standard deviations from PT average of healthy individuals. If PT was two standard deviations below PT mean of healthy individuals, patients were considered hyperexcitable and when PT was two standard deviations above, patients were considered hypoexcitable. In migraine subjects, all recordings were made in a headache-free interval (interictal period) of at least 48 hours after a migraine attack. As changes in hormone levels can modify the neuronal activity [21], all women performed the experiment in no more than seven days after the first day of menstrual cycle. Furthermore, as 40 min of blindfolding can also change cortical excitability [22], light deprivation was limited to 15 min.

2.2.2. Experiment 2 (therapeutic study)

Experiment 2 was conducted in a randomized, double blinded, parallel group controlled pilot trial from January 2013 to September 2013. Nineteen migraine patients with and without aura were recruited to investigate tDCS effectiveness as a preventive therapy for migraineurs and to observe whether it is able to correct the migraine cortical excitability abnormalities. Patients were randomly allocated to experimental ($n = 10$) or control group ($n = 9$). During four weeks, 12 sessions (3 times per week) of active (experimental group) or sham (control group) tDCS were administrated. Randomization procedures were generated by a noninvolved researcher using the website www.randomization.com. Patients and researchers involved in evaluations were blinded to group allocations.

Using a battery-driven constant current stimulator (NeuroConn, Germany) through a pair of saline-soaked sponge electrodes (surface 35 cm^2) we applied tDCS with a current intensity of 2 mA for 20 min, which had been demonstrated to be effective to reduce chronic pain [23]. For tDCS application, patients were instructed to sit in a comfortable chair. The polarity of current was determined based on interictal visual cortex excitability abnormalities according to the electrophysiological study (experiment 1) findings. Ergo, the electrode was positioned over the primary visual cortex (Oz; EEG 10/20 system [24] and the other electrode was placed over the vertex (Cz). Sham tDCS was performed by adjusting ramp periods at the beginning (10 s) and at the end (10 s) of stimulation to mimic initial local effects of active tDCS. The device was switched off (automatically) within 30 s [25], reducing bias and blinding patients and evaluators [26]. After treatment sessions, patients answered adverse effects questionnaire [27].

The headache diary was used as primary outcome measure in study to monitor migraine frequency and severity for a total of 90 days: 30 days before, 30 days during and 30 days after tDCS sessions. Therefore, patients were asked to fill the headache diary and register (i) the number of migraine attacks, (ii) pain intensity in a scale from 1 (light) to 3 (severe), (iii) duration of each attack (hours) and (iv) painkiller intake (dosage and drug classification). During the whole therapeutic study period, patients were allowed to use analgesic and abortive medications for migraine attacks.

TMS-elicited PTs were recorded before and after each tDCS session to monitor excitability changes of the visual cortex and used as secondary outcome measure in the study. TMS' coil positions were marked with a dermatological pen with waterproof ink to guarantee identical positions during the experiment.

2.3. Data analysis

We performed descriptive analyses to present demographic and clinical characteristics of the groups in both experiments. Depending on whether the variables were categorical or continuous, Chi-square and Student *t*-tests were employed to evaluate differences between the groups regarding their clinical characteristics at baseline and demographic data.

In the electrophysiological study, one-way ANOVA was used to analyze the difference among the groups. When appropriate, post hoc LSD