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Research paper

Effects of left primary motor and dorsolateral prefrontal cortex transcranial direct current stimulation on laser-evoked potentials in migraine patients and normal subjects

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HIGHLIGHTS

- Dorsolateral prefrontal cortex (DLPFC) and motor cortex (M1) anodal tDCS modified habituation of the N2P2 complex of Laser Evoked Potentials.
- Habituation to painful stimuli increase after DLPFC stimulation in migraine, and it is reduced after M1 stimulation in both patients and healthy subjects.
- The prefrontal cortex tDCS induces a normalization of temporal processing trigeminal pain in migraine patients.
- The motor cortex tDCS exertes an up-grading of nociceptive cortex activation.

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ABSTRACT

Migraine is characterized by an altered cortical excitability. Because transcranial direct current stimulation (tDCS) can change brain activity noninvasively, it is possible to hypothesize its efficacy in modulating pain in migraine. In this study, we compared the effects of tDCS of the left primary motor cortex (M1) and left dorsolateral prefrontal cortex (DLPFC) both on subjective pain and on evoked responses induced by laser stimulation (LEPs). Thirty-two patients and sixteen controls were randomized to receive sham stimulation and real tDCS with the anode centered over M1 or DLPFC. Laser Evoked potentials were recorded in basal, sham and tDCS conditions. We did not find significant acute changes in LEPs parameters and pain perception among subjects who received tDCS of both M1 and DLPFC. After DLPFC tDCS, we observed a significant increase of N2-P2 component habituation in migraine patients while M1 stimulation reduced it. These findings may suggest a modulation of abnormal pain processing induced by DLPFC and M1 anodal tDCS and outline the need for future investigations exploring the possible neuronal plasticity changes supporting the clinical effect on migraine.

1. Introduction

Migraine is a highly prevalent condition characterized by a dysfunction of cortical excitability. Evoked potentials studies showed that cortical responsivity fluctuates over time in relation to the migraine cycle (preictal/ictal/interictal) and to attacks frequency. The most reproducible abnormality, namely the lack of habituation, is detectable during the pain-free interval and it is usually accompanied by reduced evoked potentials amplitude changes across repetitive series of stimulation [1]. The habituation deficit is observed across several sensory modalities, including somatosensory nociceptive stimuli [2]. Interestingly, in this case, the lack of habituation persists across different migraine phases [3,4], underscoring the different cerebral processing of noxious versus innocuous stimuli [5]. Habituation is a multifactorial event of which the accompanying synaptic plastic mechanisms are still not totally elucidated. Recent studies proposed that hypofunctioning serotoninergic projections to the thalamus and cortex might cause functional disconnection of the thalamus, leading to thalamocortical dysrhythmia and reduced cortical habituation [6].

Non-invasive neurostimulation techniques may represent a valuable therapeutic opportunity for migraine: the understand-

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ing of their mechanism of action may improve their use in clinical practice, especially regard to the possible modulation of neuronal circuits involved in pain control. In this sense, the role of primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) was largely studied by means of high frequency repetitive transcranial magnetic stimulation (rTMS), which is able to enhance the activation of these cortical areas and indirectly induce an inhibition of the cortical regions involved in pain processing [7] with improvement of pain control [8,9]. In our previous experiment on effects of M1 high-frequency rTMS on laser-evoked responses in migraine, we found that this stimulation method inhibited somatic and trigeminal LEPs in patients, thus suggesting its possible clinical effect in preventing headache persistence by means of a down-regulation of nociceptive cortex activation [10]. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique based on a low intensity electric current application across the cranial surface, directed to specific brain areas, where it may induce focal changes of cortical excitability and activation of neuronal circuits [11]. It appears cheaper and less complex to be applied than TMS, being a potential opportunity for migraine treatment, pending the understanding of its mechanisms of action. TDCS is a pure neuromodulation technique: cathodal tDCS inhibits neuronal firing whereas anodal stimulation increases it [11]. tDCS, therefore, causes polarity-dependent shifts of the resting membrane potential and consequently could change neuronal excitability at the site of stimulation and in the connected areas. [12]. There are growing evidence about the clinical efficacy of multiple anodal DLPFC and M1 tDCS session on chronic pain, with a prevalent evidence of motor cortex stimulation value [13,14].

The tDCS of the DLPFC was demonstrated to raise the pain threshold in healthy subjects and relieve chronic pain [15,16], probably acting by changes in both the affective and sensory pain-related experience. Pain pathways function was frequently explored in migraine employing laser evoked potentials (LEPs), giving that laser stimulation activates selectively Aδ and C fibers and generates a cortical potential recordable from the temporal regions (early components) and the vertex (late components) of the skull [17]. These potentials are indicative of main pain processing steps, the early component being generated in the secondary somatosensory cortex while the late component in the insular and anterior cingulate cortex [18]. These cortical responses seemed particularly interesting for the study of migraine and indeed they allowed to show pain processing dysfunction during the critical phase [19,20] as well as in chronic migraine [21], and its possible modulation by pharmacological and non-pharmacological interventions [22,10].

In order to better define the possible mechanism of action and a potential therapeutic efficacy in migraine, in this sham-controlled study, we aimed to examine the effects of a single tDCS session of left primary motor cortex and DLPFC on laser-evoked responses. LEPs were obtained by the contralateral hand and trigeminal zone in a cohort of migraine without aura patients during the inter-critical phase, and in healthy controls. Considering the importance of habituation pattern in migraine pathophysiology, and its potential role in the mechanism of pain control, we focused on the tDCS effect on LEPs habituation paradigm in patients and control groups too.

2. Methods

2.1. Subjects

Thirty-two right handed migraine without aura patients (International Classification of Headache disorders ICHD II criteria – cod. 1.1) [23] were enrolled for the electrophysiological study and randomly assigned to M1 or DLPFC anodal tDCS task with 1:1 computer based assignation. Sixteen right-handed controls were also included and randomly assigned to M1 and DLPFC anodal tDCS task. For healthy controls exclusion criteria were: a personal and familial history of a recurrent headache, child migraine equivalents (motion sickness, cyclic vomiting or recurrent abdominal pain, somnambulism) and chronic pain syndromes. For all the included subjects, analgesics intake in the last 48 h at the time of recording, CNS acting drugs intake (including preventive treatment for migraine) in the last three months, co-morbidity for general medical and neurological or psychiatric disease, contra-indications to tDCS neurostimulation, (as metal prosthetics in the head or internal stimulation like a pacemaker, seizures history) were causes of exclusion. The distribution case-control was 2 patients for 1 control, for the difficulty in finding subjects with clear absence of familiarity and symptoms of any type of primary headache. Migraine patients were recorded during the inter-critical phase at least 72 h after the last attack and 48 h before the next one, as ascertained by a telephone interview. However in migraine group, 1 patient was excluded for attack occurrence in the proximity of recording. The demographic and clinical features of patients and controls included in the analysis are detailed in Table 1.

Table 1
Demographic and clinical features of Migraine without aura patients and controls. Results of Anova and chi square test are in table.

		Sex	Age (years)	Migraine attacks/month
M1 tDCS				
Migraine	15	5 M–11 F	35.6 ± 10.7	6.2 ± 3.1
Controls	8	2 M–6 F	37.2 ± 9.7	
		Chi square	ANOVA	
		1.34 n.s.	1.11 n.s	
DLPFC tDCS				
Migraine	16	4M–12 F	35.5 ± 9.9	5.9 ± 2.1
Controls	8	2 M – 6 F	36.0 ± 11.8	
		Chi square	ANOVA	ANOVA
		1.22 n.s.	1.21 n.s	0.88 n.s.

2.2. tDCS procedure

One session of anodal tDCS lasting 20 min at 2 mA intensity was delivered by a battery driven-DC-Stimulator MC (Neuro Conn, GmbH) using a pair of surface rubber electrodes with an extension of 7 × 5 cm in NaCl-solution soaked sponge. Fifteen migraineurs received a stimulation of left M1 by positioning the anode on the scalp in correspondence of C3 (International 10–20 System) and the cathode on the right supraorbital region. In the remaining 16 migraine patients, anodal tDCS was delivered on the left DLPFC by placing the anode on the scalp at F3 and the cathode over the right supraorbital region. Among the control subjects, 8 received tDCS of the left M1 and 8 the tDCS of the left DLPFC according to the above-mentioned parameters of stimulation. We induced the sham stimulation by fixing the tDCS electrodes in the same location on the scalp as for the real stimulation, and switching on the current for 30 s, and then we left the stimulator in place without delivering any stimulus for further 20 min.

2.3. Laser- evoked potentials

During LEP recording, the subjects laid on a couch in a warm, semi-darkened room and were awake and relaxed with their eyes open. We recorded LEPs using 21 surface recording electrodes placed on the scalp referred to the nasion, according to the International 10–20 System, by means of a MICROMED EEG apparatus (Micromed Brain Quick, Mogliano Veneto, Italy). Two additional electrodes were positioned above the eyebrows for the electrooculogram (EOG) recording; the ground electrode was located at Fpz.