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ORIGINAL ARTICLE

Safety and effects on motor cortex excitability of five cathodal transcranial direct current stimulation sessions in 25 hours

Filippo Zappasodi[a,b], **Gabriella Musumeci**[c], **Riccardo Navarra**[a,b], **Vincenzo Di Lazzaro**[c], **Massimo Caulo**[a,b], **Antonino Uncini**[a,*]

[a] *Department of neuroscience, imaging and clinical sciences, university ''G. d'Annunzio'', via L. Polacchi 11, 66100 Chieti, Italy*
[b] *Institute for advanced biomedical technologies (ITAB), university ''G. d'Annunzio'', via L. Polacchi 11, 66100 Chieti, Italy*
[c] *Unit of neurology, neurophysiology, neurobiology, department of medicine, università Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy*

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Magnetic resonance spectroscopy;
Motor evoked potentials;
Inter- and intra-individual variability

Summary
Objective. — To assess the safety and effects on motor cortex excitability of five cathodal-tDCS sessions (charge density 342.9 C/m^2) delivered over the dominant motor cortex with a return electrode over the ipsilateral shoulder at increasing time intervals in 25 hours.
Methods. — Safety was operatively defined as absence of serious adverse events related to tDCS including brain tissue alterations documentable by magnetic resonance imaging and spectroscopy. Effects on motor cortex excitability were evaluated by motor evoked potential (MEP) amplitude.
Results. — Thirty-two healthy subjects were enrolled. No serious adverse events occurred. Magnetic resonance imaging and spectroscopy did not show alterations. Inter-individual MEP variability was assessed by the standard error of mean at baseline and subjects were classified on the basis of the ratio between normalized MEPs after the first stimulation compared to baseline. Fifty-six percent of subjects responded with reduction of MEP amplitude, 25% were non-responders and 19% were inverse responders. In responders, MEP suppression was 32% one hour after the end of first cathodal-tDCS, 21% three hours after the second, no longer present with increasing stimulation intervals and 38% two and half hours after the fifth stimulation. Intra-individual inter-sessional reliability in response was high (88–92%).

* Corresponding author.
E-mail address: uncini@unich.it (A. Uncini).

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Conclusions. — Five cathodal-tDCS sessions in 25 hours are safe. Inter-individual variability in MEP suppression is considerable but response to one cathodal-tDCS highly predicts the response to other sessions. Duration of MEP suppression is limited to three hours. These findings should be considered in trials utilizing repeated cathodal-tDCS.

Introduction

Transcranial direct current stimulation (tDCS) is increasingly used for therapeutic purposes in neurological and psychiatric diseases [23,25]. TDCS induces modulation of primary motor cortex excitability, assessed by evaluation of motor evoked potentials (MEPs) after transcranial magnetic stimulation (TMS), which outlast the duration of stimulation [32—34]. Anodal stimulation has been thought to enhance motor cortical excitability, whereas cathodal stimulation to reduce it and the direct recording of the epidural activity evoked by TMS before and after tDCS has confirmed that modulatory effects take place in central motor circuits [15,24]. To obtain a greater effect in behavioral and neurophysiological outcome measures, duration and intensity of stimulations have been increased. However, the relationship between duration and intensity of the stimulation and the strength of the after-effect is more complex than initially believed. Reversal of polarity-specific effects was observed for anodal tDCS when duration of stimulation was doubled from 13 to 26 minutes and for cathodal tDCS when current intensity was doubled from 1 to 2 mA [3,29]. Another possibility to prolong the after effects is to employ repeated tDCS sessions. Anodal tDCS has been proposed for treatment of depression and in stroke rehabilitation once a day over a time period of several weeks [5,6]. It is, however, unclear whether this repetition rate is optimal to obtain the greatest efficacy, and intensive protocols employing repetitive transcranial magnetic stimulations have already been proposed in medication-resistant depressed patients [2,19]. Moreover, the possibility to safely deliver closely repeated cathodal tDCS (C-tDCS) sessions might be desirable in some fields of application such as epilepsy [18,43], or in the attempt to translate into humans the promising neuroprotective effects found in the acute stroke phase in rodents [35,38]. Therefore we designed a study to assess the safety and the effects on motor cortex excitability of five closely repeated C-tDCS sessions in 25 hours.

Methods

Subjects

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of ''G. d'Annunzio'' University of Chieti-Pescara. All subjects signed written informed consent prior to testing. Exclusion criteria included standard contraindications for tDCS and TMS such as implants, history of seizures, psychiatric or neurological disorders, and intake of medication that can modify cortical excitability [4,40]. Thirty-two healthy volunteers (19 males, age: 24.1 ± 4.2) years, were enrolled in the study. Handedness was ascertained using the Edinburgh Handedness Inventory [36].

Study plan

The overall experimental plan is shown in Fig. 1.

Magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (1H-MRS) were performed three times: the day before the first C-tDCS stimulation (17:00), within 30 min after the third C-tDCS, and within 5 hours from the fifth C-tDCS.

C-tDCS was delivered five times: the first stimulation (S1) at 9:00, the second stimulation (S2) two hours later (11:00), the third (S3) four hours from S2 (15:00), the fourth (S4) five hours from S3 (20:00) and the last (S5) was delivered the day after (10:00), 14 hours from the fourth and 25 hours after the first stimulation.

TMS evaluation was performed six times: immediately before each one of the five stimulations (T0, T1, T2, T3, T4) and the last two and half hours from the end of S5 (T5).

No sham condition was included because the goal of the study was to assess the safety and the effects on cortical excitability of repeated C-tDCS in the same subjects.

Safety and tolerability

Safety was operatively defined according to recent guidelines as the absence of serious adverse events described as severe or medically significant, even if not immediately life-threatening, events including the requirement of hospitalization and brain tissue alterations related to tDCS [1,4]. Safety and tolerability were assessed by a modified Italian version of a questionnaire proposed by Fertonani et al., 2015 (Supplementary material) [17]. To evaluate the local effect of C-tDCS the skin under the electrodes was examined before and after each stimulation.

To detect brain tissue alterations, MRI was performed using a 3-Tesla scanner equipped with a 8-channel receiver SENSE head coil (Philips Achieva, The Netherlands). First, a 3D acquisition of the whole brain was obtained using a 1-mm T1-weighted FFE sequence. Then 3 mm axial T2-weighted fluid-attenuated inversion recovery (T2w FLAIR), diffusion-weighted (DWI) and susceptibility-weighted (SWI) images were obtained. In addition, for DWI a spherical ROI was positioned on the hand area of the motor cortex of the left hemisphere to calculate the apparent diffusion coefficient (ADC) using advanced workstation software (Philips Medical Imaging System). FLAIR, DWI and SWI images were examined in real time by an experienced neuroradiologist (MC) to eventually halt the protocol if necessary minimize risk to

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