NeuroImage 83 (2013) 569–580

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Excitability modulation of the motor system induced by transcranial direct current stimulation: A multimodal approach

Maria Concetta Pellicciari [a], Debora Brignani [a], Carlo Miniussi [a,b,*]

[a] Cognitive Neuroscience Section, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[b] Department of Clinical and Experimental Sciences, National Institute of Neuroscience, University of Brescia, Brescia, Italy

ARTICLE INFO

Article history:
Accepted 29 June 2013
Available online 9 July 2013

Keywords:
tDCS
Motor cortex
Cortical reactivity
TMS
EEG
Reaction time

ABSTRACT

Anodal and cathodal transcranial direct current stimulations (tDCS) are both established techniques to induce cortical excitability changes. Typically, in the human motor system, such cortical modulations are inferred through changes in the amplitude of the motor evoked potentials (MEPs). However, it is now possible to directly evaluate tDCS-induced changes at the cortical level by recording the transcranial magnetic stimulation evoked potentials (TEPs) using electroencephalography (EEG).

The present study investigated the modulation induced by the tDCS on the motor system. The study evaluates changes in the MEPs, in the amplitude and distribution of the TEPs, in resting state oscillatory brain activity and in behavioral performance in a simple manual response task. Both the short- and long-term tDCS effects were investigated by evaluating their time course at ~0 and 30 min after tDCS.

Anodal tDCS over the left primary motor cortex (M1) induced an enhancement of corticospinal excitability, whereas cathodal stimulation produced a reduction. These changes in excitability were indexed by changes in MEP amplitude. More interestingly, tDCS modulated the cortical reactivity, which is the neuronal activity evoked by TMS, in a polarity-dependent and site-specific manner. Cortical reactivity increased after anodal stimulation over the left M1, whereas it decreased with cathodal stimulation. These effects were partially present also at long term evaluation.

No polarity-specific effect was found either on behavioral measures or on oscillatory brain activity. The latter showed a general increase in the power density of low frequency oscillations (theta and alpha) at both stimulation polarities.

Our results suggest that tDCS is able to modulate motor cortical reactivity in a polarity-specific manner, inducing a complex pattern of direct and indirect cortical activations or inhibitions of the motor system-related network, which might be related to changes in synaptic efficacy of the motor cortex.

Introduction

Several studies have endorsed the use of transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, to modulate cortical excitability (Nitsche et al., 2008) and induce neuroplasticity that is associated with cognitive and behavioral changes (Arul-Anandam and Loo, 2009; Boggio et al., 2007; Miniussi et al., 2008; Wagner et al., 2007; Wassermann and Grafman, 2005). As directly shown in animal studies, anodal tDCS increases cortical excitability, inducing a depolarization of the resting membrane potential and increasing neuronal firing rates. In contrast, cathodal tDCS decreases cortical excitability, shifting the resting membrane potential towards hyperpolarization and reducing the firing rate of neurons (Bindman et al., 1964a; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). The involvement of mechanisms similar to those underlying long-term potentiation (LTP) and long-term depression (LTD) was hypothesized to explain the tDCS induced neuroplasticity after-effects (Liebetanz et al., 2002; Nitsche et al., 2003b; Nitsche et al., 2004). The changes in neurophysiologic excitability induced by tDCS over the human primary motor cortex (M1) and their underlying mechanisms have been indirectly inferred by assessing the modifications in the excitability of the corticospinal tract using transcranial magnetic stimulation (TMS) protocols (Lang et al., 2011; Nitsche and Paulus, 2000; Nitsche and Paulus, 2001; Nitsche et al., 2005; Priori et al., 1998). Specifically, when tDCS is applied over M1, the main effect observed is an increase in the amplitude of the motor evoked potential (MEP) in the contralateral hand muscles after anodal stimulation, and a decrease after the cathodal one (Nitsche and Paulus, 2000; Nitsche and Paulus, 2001). To overcome the limitations of this indirect approach, several studies have focused their attention on other neurophysiologic measurements as surrogate markers of tDCS-induced

Abbreviations: tDCS, transcranial direct current stimulation; TEP, transcranial magnetic stimulation evoked potential; LMFP, local mean field power.

* Corresponding author at: Neuroscience Section, Department of Clinical and Experimental Sciences, University of Brescia, Viale Europa 11, 25123 Brescia, Italy. Fax: +39 0303717443.

E-mail address: carlo.miniussi@cognitiveneuroscience.it (C. Miniussi).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.06.076

cortical neuromodulatory effects (Brunoni et al., 2011). In this framework, the use of neuroimaging methods, such as functional magnetic resonance (Baudewig et al., 2001; Jang et al., 2009; Kwon et al., 2008; Polania et al., 2012; Stagg et al., 2009a), positron emission tomography (Lang et al., 2005; Paquette et al., 2011), laser doppler flowmetry (Wachter et al., 2011) and electroencephalography (EEG) (Ardolino et al., 2005; Polania et al., 2010a), have provided further evidence of changes in neural activity induced by tDCS. Moreover, it is understood that, by modulating cortical excitability, tDCS can induce both short- and long-term changes in a polarity-specific manner (Nitsche and Paulus, 2001, Nitsche et al., 2003a). Even if these results highlighted further aspects of tDCS' ability to modulate brain activity, no one, to date, has directly demonstrated current polarity-specific changes induced by tDCS on cortical, peripheral and behavioral measures of the primary motor cortex.

Starting from this scenario, we investigated polarity-dependent tDCS-induced effects using a multimodal experimental approach. Motor system changes in excitability were indexed by the following measures: MEPs, TMS-evoked potentials (TEPs), EEG frequency analyses and motor behavioral reaction times (RTs). Data were collected from healthy participants before and after the application of anodal and cathodal stimulations. A further goal of this study was to investigate short and long-lasting tDCS effects by evaluating the time course of induced changes at ~0 and 30 min after tDCS. We employed TMS-evoked cortical responses (i.e., TEPs) as a novel probe of tDCS-induced cortical excitability changes (Ilmoniemi et al., 1997; Komssi and Kahkonen, 2006; Miniussi and Thut, 2009; Miniussi et al., 2012).

Combining EEG during TMS allowed the assessment of the local impact of tDCS on neural processing through objective measurements of the cortical reactivity, reflecting the direct activation of the cortical neurons at the site of the stimulation. We used this approach to study the reactivity of the motor cortex using the amplitude of the TEPs to test the overall state of the cortex stimulated by tDCS. In addition, we evaluated the tDCS-polarity dependent changes in the stimulated left as well as in the contralateral M1, with the hypothesis that tDCS might, not only induce site-specific, but also, remote (not-site limited) effects.

Materials and methods

Subjects

Eighteen healthy participants took part to the study. Two participants were excluded from the analysis due to excessive noise in the EEG recording. The remaining sixteen participants (8 males and 8 females) had a mean age of 23.2 $\pm$ 3 years. None of the participants had a history of neurological, psychological or other relevant medical disease. None of the participants were on CNS-active medication at the time of the experiment and none had any contraindication for TMS (Rossi et al., 2009). The same criteria were also applied for tDCS. In addition, all participants were right-handed according to the Edinburgh Handedness Inventory test (Oldfield, 1971). The study was approved by the CEIOC Ethics Committee of IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Informed consent was obtained from all participants before the experiment.

Experimental design

Each participant took part in two experimental sessions during which they received anodal and cathodal tDCS, respectively. The order of tDCS polarity conditions (anodal vs. cathodal) was counterbalanced among participants. The two experimental sessions were conducted on the same day (morning and afternoon). The schedule was kept constant across participants (11:30 am and 3:30 pm) to control for potential circadian effects (Sale et al., 2007). Fig. 1 shows the experimental protocol.

To re-establish baseline levels of excitability, a 4-hour break between the two tDCS conditions was planned. During the pause between experimental conditions, participants were awake but relaxed, and were allowed to perform their own preferred relaxation activities under direct experimenter supervision.

Both the corticospinal excitability and the cortical reactivity were investigated recording the MEPs and the TEPs respectively, whereas the cortical state, indexed by oscillatory activity, was evaluated recording EEG activity during a resting state. Reaction times (RTs) were recorded during a simple detection task to evaluate the tDCS-induced effects on the behavioral performance.

All the measures were collected for each experimental session before the tDCS (baseline) and at two time points after the tDCS, i.e., immediately after (post 1) and 30 min later (post 2).

To provide the baseline measures, each experimental session began with a TEP–MEP block, followed by an EEG block and finally by a behavioral block. In each TEP–MEP block, 100 single TMS pulses were applied at a random inter-stimulus interval of 0.25–0.5 Hz with an intensity of 110% of the RMT. The TEP–MEP block lasted approximately 5 min. Each EEG block consisted of 3 min recording during a resting state with eyes open. In the behavioral block, participants performed a simple RT visual detection task that lasted approximately 5 min. After tDCS, TEP–MEP, EEG and behavioral blocks were acquired at post 1 and post 2.

During the experiment, participants were seated on a dedicated, comfortable armchair in a Faraday-cage, sound-proofed room. During TEP–MEP and EEG blocks, participants were instructed to keep their hands completely relaxed, passively sitting and fixing their eyes on a visual target directly in front of them. Each experimental session lasted approximately 75 min.

tDCS

The stimulation was delivered by a battery-driven electrical stimulator (NeuroConn GmbH, Ilmenau, Germany) through a couple of conductive-rubber electrodes placed inside saline-soaked sponges (electrode surface 25 cm^2). For anodal and cathodal stimulations, the current was delivered with an intensity of 1 mA (current density 0.04 mA/cm^2) for 13 min, with a ramping period of 8 s both at the beginning and at the end of the stimulation. The active electrode was placed over the motor cortical representational field of the right first dorsal interosseous muscle (FDI), as defined by means of a TMS mapping experiment (see below). The reference electrode was placed over the right frontopolar cortex (above the eyebrow). The electrodes were oriented approximately parallel to the central sulcus and the eyebrow. This montage was chosen because it has been shown to be effective in modulating corticospinal excitability from M1 in a polarity-specific fashion (Moliadze et al., 2010; Nitsche and Paulus, 2000; Nitsche and Paulus, 2001). The terms “anodal” and “cathodal” refer to the polarity of the electrode placed over the left M1. Before fixing the electrodes with elastic bands, an electro-conductive gel was applied under the saline-soaked sponges to reduce contact impedance. The participants were blind to the tDCS conditions.

TMS

Single pulse TMS was carried out by a Magstim SuperRapid magnetic stimulator connected to one booster module and a standard figure-of-eight shaped coil with an outer winding diameter of 70 mm (Magstim Company, Whitland, UK) that generates 2.2 T as a maximum output. In the present protocol, individual biphasic stimuli were employed. The coil was placed tangentially to the scalp, the handle pointing backwards and laterally, about a 45° angle from the mid-sagittal axis of the participants' heads and oriented to elicit a posterolateral–anteromedial current flow in the brain tissue. The stimulation started at a supra-threshold intensity. The optimal stimulus site to elicit MEPs in the right FDI, termed the “motor hotspot”, was identified by positioning the coil approximately over the central sulcus and moving it on the scalp by 0.5 cm steps on left M1. The hotspot was then marked directly on the scalp