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Effects of transcranial direct current stimulation on the functional coupling of the sensorimotor cortical network

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ABSTRACT

Transcranial direct current stimulation (tDCS) is well established—among the non-invasive brain stimulation techniques—as a method to modulate brain excitability. Polarity-dependent modulations of membrane potentials are detected after the application of anodal and cathodal stimulation, leading to changes in the electrical activity of the neurons. The main aim of the present study was to test the hypothesis that tDCS can affect—in a polarity-specific manner—the functional coupling of the sensorimotor areas during the eyes-open resting condition as revealed by total EEG coherence (i.e., coherence across the average of all combinations of the electrode pairs placed around the stimulation electrode). The changes in the total EEG coherence were evaluated pre-, during, and post-anodal and cathodal tDCS. While no differences were observed in the connectivity characteristics of the two pre-stimulation periods, a connectivity increase was observed in the alpha 2 band in the post-anodal tDCS with respect to pre-anodal and post-cathodal tDCS. The present study suggests that a specific approach based on the analyses of the functional coupling of EEG rhythms might enhance understanding of tDCS-induced effects on cortical connectivity. Moreover, this result suggests that anodal tDCS could possibly modify cortical connectivity more effectively with respect to cathodal tDCS.

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Introduction

Transcranial direct current stimulation (tDCS) is well established—among the non-invasive brain stimulation techniques—as a method to modulate neural activity. Polarity-dependent modulations of membrane potentials are detected after the application of anodal/cathodal stimulation, as reflected by a transient increase/decrease of cortical excitability (Bindman et al., 1964; Nitsche and Paulus, 2000; Paulus, 2011).

Altering brain functions with tDCS while simultaneously assessing those functions with neuroimaging is essential to determining whether and how tDCS affects brain functions. Modulation of sensorimotor function associated with tDCS has been previously investigated through several neuroimaging procedures (e.g., functional magnetic resonance imaging—fMRI, electroencephalographic—EEG spectral analysis, coregistration of transcranial magnetic stimulation, and EEG—TMS-EEG), to track the involvement of complex excitatory and inhibitory processes (Hunter et al., 2013). Moreover, changes induced by tDCS over several neurophysiological outcome measures have also been investigated (Stagg and Nitsche, 2011; Nitsche et al., 2008).

Methods directly probing the cortical activity changes underlying the polarity-induced effects of tDCS aim to investigate the overall correlations between specific neural network recruitment and behavioural changes (Shafi et al., 2012; Luft et al., 2014; Bestmann et al., 2014; Bortoletto et al., 2015a, 2015b). In order to achieve this goal, the study of cortical activity and connectivity—pre-, during, and post-tDCS—by means of EEG, operates as an important tool for correlating time-varying dynamic changes in brain connectivity/excitability with transient behavioral modifications (Keeser et al., 2011; Zaehle et al., 2011; Notturno et al., 2014). Recent studies have highlighted that different EEG measures (e.g., evoked potentials, event-related desynchronization/synchronization, and functional connectivity) can be used to probe the state of the cortical area stimulated by tDCS by adopting a multimodal approach that combines tDCS with EEG, both off- and online (e.g., Matsumoto et al., 2010; Polania et al., 2010; Pellicciari et al., 2013; for a review, see Miniussi et al., 2012). Specifically, tDCS has enabled the modulation, in a polarity-dependent manner, of local neural activity, altering ongoing brain activity in the frequency domain—with topographic dependency

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as a function of the stimulated sites (Antal et al., 2004; Spitoni et al., 2013; Mangia et al., 2014; Song et al., 2014).

The above results suggest the hypothesis that neuronal networks—as reflected by EEG activity across regional brain structures—could be modulated by tDCS (Luft et al., 2014). In this theoretical framework, the spectrum of EEG power density *per se* may not fully capture the modulation of functional neural connectivity. Nevertheless, more specific markers of functional neural connectivity can be derived by measuring the functional coupling of resting state EEG rhythms between pairs of electrodes. In fact, linear components of such coupling, functional coordination, and mutual information exchange can be evaluated by analyzing EEG spectral coherence (Gerloff et al., 1998; Gevins et al., 1998; Thatcher et al., 1986; Rappelsberger and Petsche, 1988). Spectral coherence is a normalized value that quantifies the temporal synchronization of two EEG time series between pairs of electrodes in the frequency domain of the oscillations. Its theoretical assumption is based on the observation that when the oscillatory activity of two cortical areas is functionally coordinated their EEG rhythms show a linear correlation and high spectral coherence. In general, decreased coherence either reflects reduced linear functional coupling and information transfer (i.e., functional uncoupling or unbinding) among cortical areas or reflects the reduced modulation of areas functionally bound by a third region. Conversely, an increase in EEG spectral coherence values can be interpreted as an enhancement of the linear functional connections and information transfers (i.e., functional coupling or binding), reflecting the interaction of individual cortical structures. Increased coherence in alpha or in faster EEG frequencies reflects a greater "facilitation," or functional connectivity. Meanwhile, increased coherence in the delta frequency suggests a greater "inhibition," or a functional disconnection. Pertinently, spectral coherence may reflect the integrity of cortical neural pathways (Locatelli et al., 1998). Previous EEG studies have reported a greater decrease of coherence for alpha rhythms and an increase for delta rhythms in cognitively impaired patients than in control subjects—as an effect of the brain network's disconnection (Cook and Leuchter, 1996; Jelic et al., 1997, 2000; Almkvist et al., 2001; Knott et al., 2000; Adler et al., 2003). Moreover, changes of motor cortex excitability, tested by TMS, can be predicted by evaluating the EEG fluctuations of the motor cortex connectivity patterns in the period preceding the delivery of the TMS pulse (Ferreri et al., 2014). It has also been demonstrated that EEG spectral coherence is enhanced following perceptive, cognitive, and motor processes in the cortical regions involved in task-related processing (Sauseng et al., 2005; Vecchio et al., 2007, 2010, 2012). This occurs as a function of the extension and type of the engaged neural networks (Pfurtscheller and Lopes da Silva, 1999; Von Stein and Sarnthein, 2000). In addition, recent studies introduced the concept of "total coherence," obtained by averaging the EEG spectral coherence across all combinations of electrode pairs (Tecchio et al., 2003, Babiloni et al., 2010, 2014).

The present work is the logical sequel of a previous study that addressed the hypothesis of specific cortical excitability modulations induced by the different polarity of tDCS (e.g., Pellicciari et al., 2013). It also stems from studies showing that anodal tDCS alters ongoing brain EEG activity during resting state, in the alpha band rhythm (e.g., Spitoni et al., 2013). Here, we tried to demonstrate that tDCS induces brain network modulation, particularly pertaining to the functional coupling of the alpha rhythm, moving from the evidence of a statistically significant influence of time-varying and spatially patterned synchronization of EEG rhythms in determining cortical excitability (Ferreri et al., 2014). Moreover, the activity of pyramidal cortical neurons, which contribute to the excitability levels of the related neuronal assemblies, can be inferred by EEG scalp characteristics, such as spectral frequency profiles, topographies of various rhythms, and the phase coherence of the EEG oscillations (Ferreri et al., 2011a, 2011b, 2012; Klimesch et al., 2007; Neuper and Pfurtscheller, 2001).

Given these premises, the choice to investigate the coupling of the sensorimotor areas via EEG recording during the resting state was based on the idea that this coupling might predominately involve the alpha rhythm. Therefore, the main aim of the present study was to test the hypothesis that a specific tDCS current polarity affects the functional coupling of sensorimotor areas during the eyes-open resting condition, as revealed by the total EEG coherence (i.e., coherence across the average of all combinations of electrode pairs placed around the scalp stimulation electrode; this allows for the observation of a global modulation of coupling in the considered network) recorded before (pre), during, and after (post) anodal and cathodal stimulation.

Materials and methods

Subjects

Eighteen healthy participants took part in the study. Three participants were excluded from the analysis due to excessive noise in the EEG recording during tDCS. The remaining fifteen (seven males and eight females) had a mean age of 23.2 ± 3 years. The inclusion criteria were as follows: no history of neurological, psychological, or other relevant medical diseases and no consumption of CNS-active medication at the time of the experiment. The study was approved by the Ethics Committee of IRCCS Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy, and written informed consent was obtained from all participants before the experiment.

Experimental design

Each participant took part in two experimental sessions, during which anodal and cathodal tDCS were delivered, respectively. The order of tDCS polarity conditions was counterbalanced among participants. The two experimental sessions were conducted on the same day (with a 4-h break between the two tDCS conditions), and the schedule was kept constant across participants to control for potential circadian effects (Sale et al., 2007). Fig. 1 shows the experimental protocol.

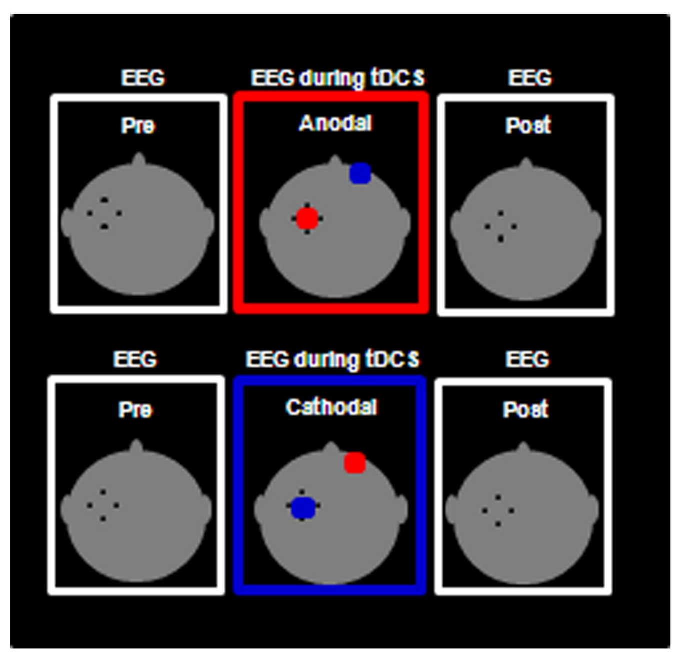

Fig. 1. Experimental procedure. Each experimental session consisted of an EEG block before (3 min), during (13 min), and after tDCS (3 min). Each block consisted of a EEG activity recording during a resting state with eyes open. Anodal and cathodal tDCS were applied to the left primary motor cortex in separate sessions, on the same day (with a 4-h break between the two tDCS conditions). Direct current stimulation (1 mA) was given through two large-sized electrodes placed (25 cm^2) over M1 and the contralateral frontopolar cortex.

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