NeuroImage 157 (2017) 34–44

Contents lists available at ScienceDirect

NeuroImage

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

Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex

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A R T I C L E I N F O

Keywords:
FMRI
Resting state
Functional connectivity
Transcranial direct current stimulation
Network stimulation

A B S T R A C T

Scientists and clinicians have traditionally targeted single brain regions with stimulation to modulate brain function and disease. However, brain regions do not operate in isolation, but interact with other regions through networks. As such, stimulation of one region may impact and be impacted by other regions in its network. Here we test whether the effects of brain stimulation can be enhanced by simultaneously targeting a region and its network, identified with resting state functional connectivity MRI. Fifteen healthy participants received two types of transcranial direct current stimulation (tDCS): a traditional two-electrode montage targeting a single brain region (left primary motor cortex [M1]) and a novel eight-electrode montage targeting this region and its associated resting state network. As a control, 8 participants also received multifocal tDCS mismatched to this network. Network-targeted tDCS more than doubled the increase in left M1 excitability over time compared to traditional tDCS and the multifocal control. Modeling studies suggest these results are unlikely to be due to tDCS effects on left M1 itself, however it is impossible to completely exclude this possibility. It also remains unclear whether multifocal tDCS targeting a network selectively modulates this network and which regions within the network are most responsible for observed effects. Despite these limitations, network-targeted tDCS appears to be a promising approach for enhancing tDCS effects beyond traditional stimulation targeting a single brain region. Future work is needed to test whether these results extend to other resting state networks and enhance behavioral or therapeutic effects.

Introduction

Scientists and clinicians have traditionally used brain stimulation, both invasive and noninvasive, to target single regions in order to modulate brain function and disease (Nitsche and Paulus, 2000; Nitsche et al., 2003; Fox et al., 2014; Wang et al., 2014; Eldaief et al., 2013; Brunoni et al., 2012). Stimulating primary motor cortex, for example, can increase corticospinal excitability (Nitsche and Paulus, 2000; Horvath et al., 2014) and may improve motor symptoms in stroke and Parkinson's Disease (Horvath et al., 2014; Schlaug et al., 2008; Broeder et al., 2015). However, brain regions do not operate in isolation; they communicate with other regions, through excitatory and inhibitory interactions, in distributed brain networks (Siegel et al., 2015; Yeo et al., 2011; Sporns et al., 2004; Grefkes and Fink, 2014; Grefkes et al., 2008). It is likely that these network-level interactions are influenced by stimulation of a single site, and influence the impact of stimulation at that site (Fox et al., 2014; Wang et al., 2014; Chen et al., 2013; Volz et al., 2015; Nettekoven et al., 2015; Polanía et al.,

Abbreviations: EEG, electroencephalography; FDI, first dorsal interosseus muscle; fMRI, functional magnetic resonance imaging; M1, primary motor cortex; MEP, motor evoked potential; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation

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http://dx.doi.org/10.1016/j.neuroimage.2017.05.060
Received 12 March 2017; Received in revised form 8 May 2017; Accepted 27 May 2017
Available online 29 May 2017
1053-8119/

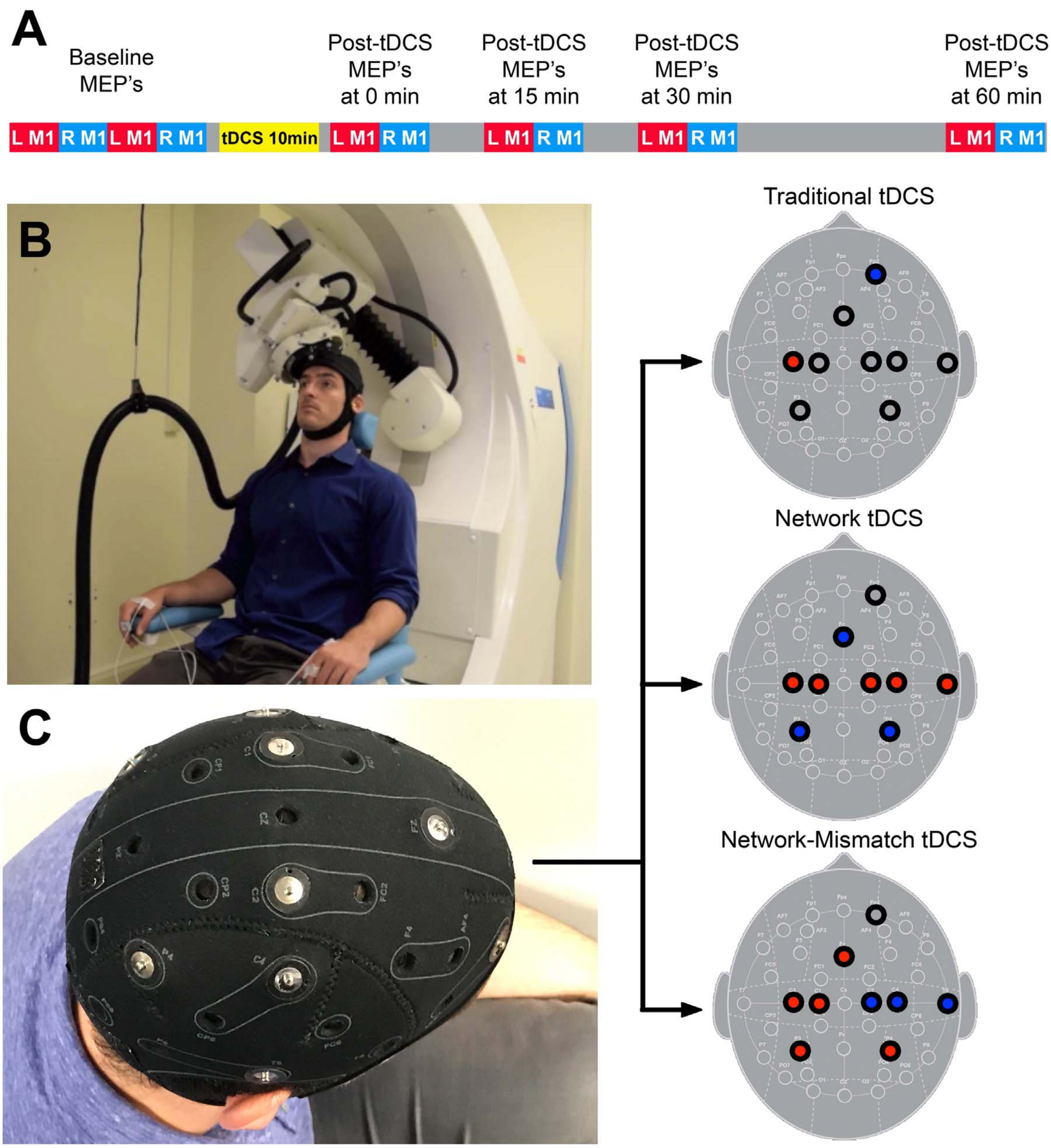

Fig. 1. Experimental design. Motor evoked potentials (MEPs) were assessed at baseline, and after tDCS at regular intervals (A). MEPs were elicited with neuro-navigated robotic TMS to optimize accuracy/precision and minimize bias (B). For all sessions, electrodes were placed in identical locations, with electrical current applied through the electrodes in one of three configurations (C): traditional tDCS (N = 15), network tDCS (N = 15), and network-mismatch tDCS (N = 8). Anodal stimulation is represented in red, cathodal stimulation in blue.

2011). For example, transcranial magnetic stimulation (TMS) administered to brain regions connected to primary motor cortex alters motor cortex excitability and its response to a subsequent TMS pulse (Kujirai et al., 1993; Koch et al., 2007; Pinto and Chen, 2001). If one simultaneously stimulated multiple brain regions connected to primary motor cortex, this could result in a larger effect on motor cortex excitability than stimulating motor cortex alone.

One type of brain stimulation potentially well-suited for targeting a distributed brain network is transcranial direct current stimulation (tDCS) (Ruffini et al., 2014; M.A. Nitsche and Paulus, 2000; Polanía et al., 2011; Polanía et al., 2012; Kuo et al., 2013). Traditionally, tDCS involves two electrodes placed on the scalp surface: a positively charged anode (thought to enhance excitability of underlying cortex) and a negatively charged cathode (thought to suppresses excitability of underlying cortex) (Nitsche et al., 2008). More recently, high-density multi-electrode tDCS arrays have become available (Caparelli-Daquer et al., 2012) and could be used to simultaneously stimulate multiple regions of a distributed brain network (Ruffini et al., 2014). One popular tool for visualizing brain networks is resting state functional connectivity MRI (rs-fcMRI), which identifies functionally associated brain areas through synchronous oscillations of spontaneous brain activity (Yeo et al., 2011; Fox et al., 2005; Fox and Raichle, 2007). Recently, we presented an algorithm for determining the optimal placement and current output of multifocal tDCS electrodes to best target a spatially distributed resting state network (Ruffini et al., 2014). However, this algorithm was based on several assumptions regarding tDCS-induced electric fields, the neurophysiological effect of these electric fields, and the interactions between brain regions within a resting state network (Ruffini et al., 2014). Whether a multifocal tDCS array targeting a brain network results in different neurophysiological effects compared to traditional tDCS targeting a single brain region remains to be tested experimentally.

Here, we conduct the first test of network-targeted stimulation, using multifocal tDCS to simultaneously stimulate left primary motor