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Research Report

Baseline effects of transcranial direct current stimulation on glutamatergic neurotransmission and large-scale network connectivity

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ABSTRACT

Transcranial direct current stimulation (tDCS) modulates glutamatergic neurotransmission and can be utilized as a novel treatment intervention for a multitude of populations. However, the exact mechanism by which tDCS modulates the brain's neural architecture, from the micro to macro scales, have yet to be investigated. Using a within-subjects design, resting-state functional magnetic resonance imaging (rs-fMRI) and proton magnetic resonance spectroscopy (^{1}H MRS) were performed immediately before and after the administration of anodal tDCS over right parietal cortex. Group independent component analysis (ICA) was used to decompose fMRI scans into 75 brain networks, from which 12 resting-state networks were identified that had significant voxel-wise functional connectivity to anatomical regions of interest. ^{1}H MRS was used to obtain estimates of combined glutamate and glutamine (Glx) concentrations from bilateral intraparietal sulcus. Paired sample *t*-tests showed significantly increased Glx under the anodal electrode, but not in homologous regions of the contralateral hemisphere. Increases of within-network connectivity were observed within the superior parietal, inferior parietal, left frontal–parietal, salience and cerebellar intrinsic networks, and decreases in connectivity were observed in the anterior cingulate and the basal ganglia ($p<0.05$, FDR-corrected). Individual differences in Glx concentrations predicted network connectivity in most of these networks. The observed relationships between glutamatergic neurotransmission and network connectivity may be used to guide future tDCS protocols that aim to target and alter neuroplastic mechanisms in healthy individuals as well as those with psychiatric and neurologic disorders.

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1. Introduction

Neuroplasticity is essential for brain development and adaptation as it enables the nervous system to reorganize neural pathways based on new experiences. Research is underway to examine ways to harness neuroplasticity in order to promote healing and recovery (see Peled, 2004; 2005; Spedding et al., 2003; and Kays et al., 2012 for review). Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that modulates the excitability of functional brain networks (Polanía et al., 2011; Keeser et al., 2011; Sehm et al., 2012; Peña-Gómez et al., 2012). It is thought to increase the spontaneous firing of cortical neurons near the anode electrode (with positive polarity) while decreasing it near the cathode (with negative polarity) (Nitsche and Paulus, 2000; Dieckhöfer et al., 2006). By modulating the excitability of glutamatergic pyramidal neurons in the underlying cortex (Radman et al., 2009), tDCS influences neurophysiological mechanisms responsible for neuroplasticity. These mechanisms involve the potentiation of synaptic glutamatergic receptors (Liebetanz et al., 2002; Nitsche et al., 2005), and decreased neurotransmission of γ-aminobutyric acid interneurons (GABA) (Nitsche et al., 2004; Stagg et al., 2009; Stagg and Nitsche, 2011; also see Medeiros et al., 2012 for review).

In particular, NMDA and AMPA receptors are essential for synaptic plasticity by influencing long-term potentiation and depression (LTP and LTD) across structurally-connected brain regions (Bliss and Collingridge, 1993). These synaptic and neuronal pathways consolidate into stable and long-lasting functional brain networks (Fricke et al., 2011; Venkatakrishnan et al., 2011; Venkatakrishnan and Sandrini, 2012). However, the effects of tDCS on glutamate levels and its relation to large-scale network connectivity have yet to be fully elucidated; that is, there must be a better understanding of how tDCS interacts across different scales within the brain's neural architecture by combining different, yet complementary, imaging modalities (see Hunter et al., 2013 for a review), which was the primary objective of the present study.

1.1. *tDCS-induced effects on neurometabolites*

Proton magnetic resonance spectroscopy (^{1}H MRS) enables quantification of certain neurometabolites within a localized region of the brain (Gruetter et al., 2001; Steen et al., 2005). This method has been used to examine the effects of tDCS on specific neurometabolites. To date, anodal tDCS has been associated with *increases* in combined glutamine and glutamate (Glx) (Stagg et al., 2009; Clark et al., 2011) and myoinositol concentrations (Rango et al., 2008). Concordantly, *reductions* have been found in GABA concentration with anodal tDCS (Stagg et al., 2009). Consistent with these findings, the activation of metabotropic glutamate receptors, in conjunction with stable long-range intrinsic membrane oscillations, has been shown to entrain local and distributed GABAergic interneurons (Whittington et al., 1995). Together, the observed changes in glutamatergic and GABAergic activity may translate to subsequent alterations in both local and distributed processing—influenced by both excitatory and inhibitory signaling pathways—in functional brain networks.

1.2. *tDCS-induced effects on network-based connectivity*

Functional magnetic resonance imaging (fMRI) is a noninvasive technique for acquiring dynamic changes in blood oxygenation, measured as the blood-oxygenation-level dependent (BOLD) signal. While at rest, spontaneous fluctuations in the BOLD signal (0.10–0.15 Hz) show high correlations across structurally connected and functionally related brain regions (Biswal et al., 1995; Skudlarski et al., 2010; see Fox and Raichle, 2007 for review). These fluctuations reflect a stable, intrinsic organization of the brain that maintains and reinforces established synaptic connections that support cognitive and behavioral functions (see Raichle and Snyder, 2007 and Van Den Heuvel and Hulshoff Pol, 2010 for reviews). The most commonly observed intrinsic network is the default-mode network (DMN), which links precuneus and posterior cingulate cortex (PCC) with bilateral inferior parietal and medial frontal cortices, with the highest activations observed in the posterior regions (Raichle et al., 2001; Greicius et al., 2003). Independent component analysis (ICA) can be used to decompose resting-state fMRI (rs-fMRI) signals into functionally related "groups" of voxels that comprise functionally connected brain networks (Erhardt et al., 2011). The strength of ICA is its ability to resolve data into maximally independent sources, thereby revealing the dynamics of intrinsic networks (McKeown et al., 1997; Calhoun et al., 2001; Beckmann et al., 2005; Calhoun et al., 2011; Calhoun and Adalı, 2012).

A recent study of anodal (2.0 mA) tDCS over the dorsolateral prefrontal cortex (DLPFC), with the cathode placed over contralateral supraorbital area, resulted in increased intrinsic functional connectivity *within* the frontal node of the DMN and the left frontal–parietal network (Keeser et al., 2011). Similarly, Peña-Gómez et al. (2012) found that this same tDCS montage produced a redistribution of ICA-generated functional network connectivity (FNC), a measure of the temporal relationship among ICA components. Increased FNC between networks that overlapped with the site of stimulation and with superior parietal networks (comprising task-related circuits) was observed; whereas a decrease in FNC was found between networks that comprise the DMN (Peña-Gómez et al., 2012). These results suggest that anodal tDCS over DLPFC may enhance the flexible balance between brain networks by enhancing network connectivity for cognitive demands while reducing its anti-correlated DMN activity.

Furthermore, a recent rs-fMRI study placed the anode over the right angular gyrus, with the cathode over contralateral supraorbital region (Clemens et al., 2014). Increases in ICA-generated functional connectivity in the cerebellum, medial occipital, sensorimotor, right frontal parietal, and superior frontal gyrus were observed, while decreases were found in the right putamen and lateral occipital areas. Furthermore, active tDCS has also contributed to both inter-hemispheric (Sehm et al., 2012; 2013; Park et al., 2013) and corticostriatal functional connectivity (Polanía et al., 2012; Clemens et al., 2014). Overall, studies that combine fMRI and tDCS show widespread changes in functional connectivity at both local