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Polarity- and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol

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Summary Recent evidence has supported the notion that the hypothalamic-pituitary-adrenal (HPA) and the sympatho-adreno-medullary (SAM) systems are modulated by cortical structures such as the prefrontal cortex. This top-down modulation may play a major role in the neuroendocrine changes associated with stressful events. We aimed to investigate further this hypothesis by modulating directly prefrontal cortex excitability using transcranial direct current stimulation (tDCS) — a non-invasive, neuromodulatory tool that induces polarity-dependent changes in cortical excitability — and measuring effects on salivary cortisol and heart rate variability as proxies of the HPA and SAM systems. Twenty healthy participants with no clinical and neuropsychiatric conditions were randomized to receive bifrontal tDCS (left anodal/right cathodal or left cathodal/right anodal) or sham stimulation, in a within-subject design. During each stimulation session, after a resting period, subjects were shown images with neutral or negative valence. Our findings showed that excitability enhancing left anodal tDCS induced a decrease in cortisol levels. This effect is more pronounced during emotional negative stimuli. Moreover, vagal activity was higher during left anodal tDCS and emotional negative stimuli, as compared to sham stimulation and neutral images. We also observed an association between higher mood scores, higher vagal

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activation and lower cortisol levels for anodal stimulation. Subjective mood and anxiety evaluation revealed no specific changes after stimulation. Our findings suggest that tDCS induced transient, polarity specific modulatory top-down effects with anodal tDCS leading to a down-regulation of HPA and SAM systems. Further research using tDCS and neuroendocrine markers should explore the mechanisms of stress regulation in healthy and clinical samples.

1. Introduction

The dorsolateral prefrontal cortex (DLPFC) has been associated with a wide range of cognitive functions from selective attention, working memory, decision-making including emotional behavior and empathy (Cerqueira et al., 2008; Damasio, 2000) to regulation of mood and anxiety (Davidson et al., 2002). In fact, one important role of DLPFC is in processing and regulating stressful, emotional responses — for instance, DLPFC shows activation when voluntarily suppressing sadness (Levesque et al., 2003) and co-activation with the amygdala during emotion reappraisal (Banks et al., 2007). Immediately following a stressful event, subcortical areas (such as the amygdala, hypothalamus and brainstem monoaminergic nuclei) trigger strong (albeit relatively unspecific) neuroendocrine responses, notably the activation of the sympatho-adreno-medullary system (SAM) and the hypothalamic-pituitary-adrenal (HPA) axis, thereby increasing noradrenaline and cortisol levels. In this context, further DLPFC neural processing may either lead to a top-down regulation, ultimately inhibiting SAM and HPA activity or, conversely, subcortical areas might down-regulate cortical activity, with subsequent increasing in SAM and HPA functioning. This latter, "bottom-up" pattern (amygdala hyperactivity/DLPFC hypoactivity) is observed in mood and anxiety disorders, both during resting state and cognitive/challenging neuroimaging and functional studies (Quide et al., 2012; Britton et al., 2011; Drevets et al., 2008). In addition, analogous to other cortical structures, DLPFC has lateralized properties: while the left side is associated with parasympathetic activity, positive emotional processing and approach behavior; the right PFC is associated with sympathetic activity, negative emotional processing and withdrawal behavior (Cerqueira et al., 2008). Indeed, mood and anxiety disorders are associated with hypoactivity of the left DLPFC (Davidson et al., 2002).

Nevertheless, most research in the field is correlational, and experimental manipulation is necessary to increase our insight in the causal relationship between cortical functioning, emotional regulation and specific stress responses. In this context, transcranial direct current stimulation (tDCS) is one interesting tool to investigate such processes. TDCS is a neuromodulatory technique that consists in applying a direct electric current through electrodes positioned over the scalp to induce local and secondarily distance neuroplasticity. Although tDCS induced current is weak, it is able to reach the neuronal tissue and induce polarization-shifts on cortical excitability (Nitsche et al., 2008; Brunoni et al., 2011c). Remarkably, anodal stimulation generally facilitates cortical activity, whereas cathodal tDCS has opposite effects (Brunoni et al., 2011c). In fact, studies have shown polarity-dependent tDCS effects for several cortical areas, including occipital, sensory, motor and prefrontal cortex areas (Utz et al., 2010).

Therefore, considering the importance of DLPFC in emotional processing and stress responses in healthy individuals as well as in neuropsychiatric disorders, we sought to test whether tDCS of DLPFC regulates emotional processes and stress responses by measuring heart rate variability (HRV) and salivary cortisol levels as they reflect SAM and HPA functioning (Marques et al., 2010). Specifically, while the former assesses the relative influences of sympathetic and vagal branches over heart beat-to-beat activity (ESC, 1996); the latter increases as a stress response to negative and unpleasant stimuli (Hellhammer et al., 2009).

In this sham-controlled study, two different montages were used: left anodal/right cathodal stimulation (thus increasing left DLPFC cortical excitability and an opposite effect on the right DLPFC) and, conversely, right anodal/left cathodal stimulation (thus inducing a contrary effect). Emotional responses were induced using images of negative valence. Based on the current knowledge in the lateralized DLFPC processing of emotional information and its top-down inhibitory properties, we hypothesized that the former montage would be associated with decreased and the latter with increased SAM and HPA activity, respectively, as indexed by HRV and cortisol measures. In despite of gaining mechanistic insights of DLPFC and tDCS functioning, this study is also important to measure safety — i.e., whether tDCS could exert hazardous effects in autonomic activity, as anecdotally reported (Redfearn et al., 1964) — and to also support the exploration of tDCS for potential clinical gains — e.g., regulation of blood pressure (Cogiamanian et al., 2010) and stress response.

2. Methods

2.1. Subjects

Twenty healthy participants with no psychiatric or clinical conditions were included. Their mean age was 24.9 (SD = 3.8) years and three were male. They were recruited among university students at the University of São Paulo, Brazil. All volunteers gave written informed consent and the local Ethics Committee approved the study. No financial compensation was given. We screened 31 subjects. Of them, a trained psychiatrist excluded those with prior and current psychiatric disorders by a psychiatrist using the M.I.N.I. questionnaire (Sheehan et al., 1998) and the Beck Depression Inventory (BDI) (Gorenstein et al., 2000) — those with scores higher than 8 were excluded ($n = 4$, with acute depressive episode and $n = 1$ with generalized anxiety disorder). In addition, we performed biochemistry, anthropometric and EKG evaluations as to exclude those with potential cardiovascular conditions ($n = 1$, with sinus bradycardia and first-degree atrioventricular block). We also excluded participants who perform intense physical activity ($n = 3$, university students