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Prefrontal anodal High Definition-tDCS has limited effects on emotion regulation

Poor emotional regulation has been associated with core symptoms of a broad spectrum of mental health problems and neurodevelopmental disorders [1,2], and is a key cognitive ability to ensure psychological well-being. Indeed, healthy emotion regulation skills are a protective factor for the development of mental health conditions in young adulthood [3].

The ventrolateral prefrontal cortex (vlPFC) has been identified as one of the key brain regions underlying successful emotion regulation [4]. Diminished activity within this region has been linked to a reduced use of adaptive emotion regulation strategies such as cognitive reappraisal (i.e., the ability to reduce negative emotional states by generating positive interpretations) [5]. Thus, the vlPFC appears to be a promising target for non-invasive brain stimulation (NIBS) techniques to enhance emotion-regulatory function in patients with affective and social disorders.

To date, only four studies have investigated the role of the vlPFC in cognitive reappraisal using transcranial direct current stimulation (tDCS [6–9]). In two of these studies, He et al., 2018, 2020 demonstrated that anodal tDCS over the right vlPFC improved reappraisal skills in the context of social exclusion in healthy participants [6], but failed to show improvements in individuals with high depressive traits [7]. Marques et al., 2018 found a reduction in the subjective valence ratings for negative images when applying anodal tDCS over the left vlPFC. Conversely, Vieira et al., 2020 showed no improvements in the subjective valence ratings for negative images following the same stimulation protocol described in Marques et al., 2018.

When it comes to the use of brain tDCS in emotion regulation, there is a need to integrate new procedures to improve the understanding of the effects of the stimulation over the vlPFC to modulate cognitive reappraisal skills. However, the current procedures fall short of achieving this due to four main challenges: (1) the lack of highly targeted stimulation protocols; (2) the need to reduce inter-individual variability among participants; (3) the need to apply brain stimulation protocols while engaging the targeted region; and (4) the selection of adequate biomarkers to accurately measure the modulation response. To achieve this, here we incorporated methods to i) reduce individual variability (i.e., within-subjects vs. between-subjects design), ii) increase focality and targeted stimulation (i.e., high definition tDCS [HD-tDCS] vs. conventional tDCS), iii) produce more robust stimulation effects with the use of a cognitive task that specifically engages the vlPFC, and iv) utilise a reliable electrophysiological marker of emotion regulation (i.e., the late positive event-related potential [LPP]).

Our study examined the effects of anodal HD-tDCS compared to sham (placebo) HD-tDCS over the right vlPFC in healthy young adults (18–25 years). We used a sham-controlled, double blind, repeated measures design, where participants completed two separate testing sessions. These sessions were at least 120 hours apart to control for carryover effects of the stimulation, and the order of HD-tDCS (anodal vs. sham) was counterbalanced across participants. Twenty-six right-handed, English-speaking individuals consented to take part in the study. Three participants were excluded for medical contraindications and four did not attend the second session due to travel difficulties and transportation time. The final sample comprised 19 participants (12 females, mean age = 22.95 years [SD = 3.27]; see Supplementary Materials, *1*). Anodal HD-tDCS was applied at 1.693mA for 20 minutes over the right vlPFC using a wireless (Bluetooth) Neuroelectrics Star Stim control box (HD-tDCS device) and corresponding NIC2 software (see Supplementary Materials, *2)*. During the administration of HD-tDCS, participants also completed the Stop Signal Task, which engages vlPFC, in an attempt to produce stronger stimulation effects (see Supplementary Materials, *3*). The study was approved by the Human Research Ethics Committee of Deakin University (Australia), and all participants provided signed informed consent.

Immediately following stimulation, emotion regulation was assessed using the cognitive reappraisal task, which asks participants to engage with or regulate the negative emotions triggered by negatively-valenced images (CRT; see Supplementary Materials, *4*). During the CRT, 64-channel electroencephalography (EEG; SynAmps RT, Compumedics Neuroscan; Abbotsford, Victoria, Australia) was recorded to measure the amplitudes of the LPP (see Supplementary Materials, *5*). The amplitude of the LPP was measured in the three main CRT conditions: 'Maintain' (sustaining the negative emotional state elicited by negative images), 'Regulate' (the ability to reappraise negative emotions), and 'Observe' (to simply observe neutral images). For the 'Regulate' condition, participants were trained to employ cognitive reappraisal strategies to reinterpret the image into positive terms. We also administered surveys measuring emotion regulation traits to factor in background individual differences and a post-stimulation questionnaire to assess HD-tDCS-related side effects (see Supplementary Materials, *6*).

Generalised linear mixed models were used to examine the effect of HD-tDCS on the LPP with Stimulation (anodal vs. sham) and Task Condition (regulate, maintain and observe) as fixed effects, and participant as a random effect. All analyses were conducted using SPSS 27.0 (IBM Corp; Armonk, NY).

The Stimulation by Condition effect on LPP amplitudes did not reach significance, $F(2, 90) = 1.81$, $p = 0.169$. Nevertheless, we conducted subsequent pairwise comparisons, based on *a priori* assumptions, to examine specific stimulation effects on the 'Regulate'

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Condition compared to 'Maintain' and 'Observe' Conditions. It was hypothesised that the latter two conditions would not be susceptible to the active stimulation of the vlPFC, as they generally do not engage emotion regulation processes. The analysis showed significant differences between 'anodal' and 'sham' stimulation on LPP amplitudes during the 'Regulate' Condition (t [18] = 2.249; p = 0.037; see Fig. 1). The significant increase in the amplitude of the LPP component, suggests a strengthening of the emotional regulation response after the stimulation. Conversely, there were no significant stimulation effects on the 'Maintain' (t [18] = 1.141; p = 0.269) and 'Observe' (t [18] = 0.078; p = 0.939) conditions.

This is the first study to investigate the effect of anodal HD-tDCS over the right vlPFC on the neural (electrophysiological) underpinnings of emotion regulation. We did not find the expected interaction effect between stimulation and task conditions, likely due to the limited sample size and lack of power [10]. However, in support of our hypothesis, we found significant stimulation effects on the 'Regulate' condition. These effects have been previously shown to be related with our neural stimulation target (vlPFC), which in our study, was associated with differences in LPP amplitudes between anodal and sham stimulation. Although these findings should be interpreted with caution, they highlight the potential beneficial effects of HD-tDCS for improving management of negative emotions. We hope this initial evidence, for the likely neurophysiological mechanism, will contribute to generate further studies in this area, which may eventually lead to clinical research to modulate affective and emotional processes in a variety of mental health conditions.

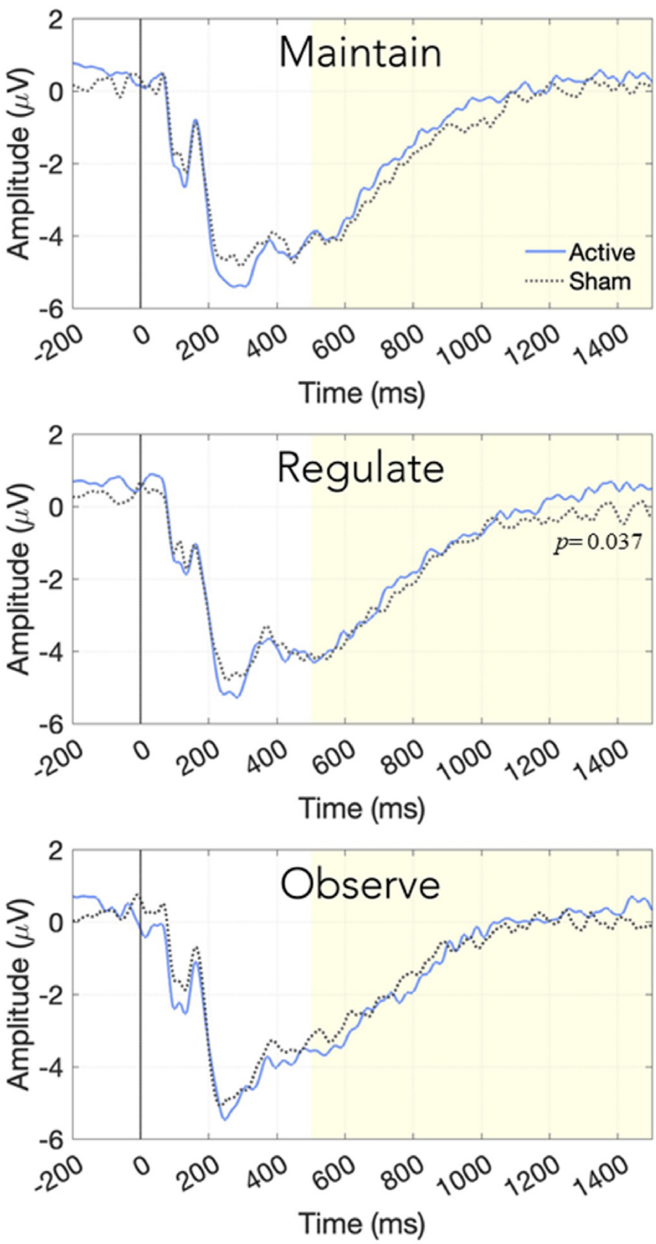

Fig. 1. Late positive potential amplitudes during the Cognitive Reappraisal Task conditions "Maintain", "Regulate" and "Observe" following High Definition-transcranial Direct Current Stimulation (HD-tDCS).

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.12.007.

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