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Dopamine depletion effects on cognitive flexibility as modulated by tDCS of the dlPFC

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Abstract

Background:

Recent evidence suggests that transcranial direct current stimulation (tDCS) may interact with the dopaminergic system to affect cognitive flexibility.

Objective/hypotheses:

We examined whether putative reduction of dopamine levels through the acute tyrosine/phenylalanine depletion (ATPD) procedure and excitatory anodal tDCS of the dorsolateral prefrontal cortex (dlPFC) are causally related to cognitive flexibility as measured by task switching and reversal learning.

Method:

A double-blind, sham controlled, randomised trial was conducted to test the effects of combining anodal tDCS and depletion of catecholaminergic precursor tyrosine on cognitive flexibility.

Results

Anodal tDCS and tyrosine depletion had a significant effect on task switching, but not reversal learning. Whilst perseverative errors were significantly improved by anodal tDCS, the ATPD impaired reaction times. Importantly, the combination of ATPD and anodal tDCS resulted in cognitive performance which did not statistically differ to that of the control condition.

Conclusions:

Our results suggest that the effects of tDCS on cognitive flexibility are modulated by dopaminergic tone.

Keywords: transcranial direct current stimulation, tDCS; dopamine depletion; flexibility; learning

1. Introduction

Changes in dopaminergic signalling have been implicated in the regulation of cognitive flexibility [1-5]. In humans, administration of the dopamine precursors L-dopa and tyrosine leads to enhanced cognitive flexibility [1, 6, 7], whereas reducing dopaminergic tone through the acute phenylalanine/tyrosine depletion procedure (APTD) impairs indices of cognitive flexibility [8, 9].

Neuroanatomically, transcranial direct current stimulation (tDCS) studies in humans have indicated that the dorsolateral prefrontal cortex (dlPFC) is an important modulator of cognitive flexibility. Whilst anodal tDCS improved cognitive flexibility performance [10, 11], cathodal tDCS worsened performance [12, 13] . Despite these findings, the effects of tDCS are highly variable because of both methodological (e.g. position of the reference/return electrode, see [14, 15] and biological heterogeneity [15]). In particular, polymorphisms in the COMT gene, which at least in part determines dopamine activity, have been associated with the effects of anodal/cathodal tDCS on indices of cognitive flexibility [16, 17]. Here, those with the lowest levels of dopamine (Val/Val homozygous) and those with the highest (Met/Met homozygous), were negatively affected by cathodal (inhibitory) and anodal (excitatory) tDCS respectively.

In line with converging evidence that tDCS may exert its behavioural effects via modulation of the dopaminergic system, anodal tDCS applied to the dlPFC increased extracellular dopamine levels in the striatum [18]. Moreover, administration of the dopamine precursor L-DOPA influences cortical excitability after cathodal tDCS in a dose-dependent manner [19, 20], whilst tyrosine modulates tDCS effects on measures of working memory [21].

These results have also prompted the suggestion of an inverted U-shaped relationship between dopamine concentration and cognitive performance. Recently, our group tested the effects of combining an increase in dopaminergic tone with tDCS on indices of cognitive flexibility [22]. In line with the inverted U-shaped model, cathodal tDCS had the most detrimental effects on

cognitive flexibility, whereas tyrosine was most beneficial to cognitive flexibility. Importantly, the combination of cathodal tDCS plus tyrosine resulted in a cognitive flexibility performance that was statistically indistinguishable from that of the control condition (sham tDCS + placebo), which provides at least some behavioural evidence of the modulation of dopaminergic tone in the effects of tDCS on cognitive flexibility.

In the current study, we further investigated the modulatory influence of dopamine on the effects of tDCS of the dlPFC on cognitive flexibility. Specifically, our goal was to substantially extend our understanding of this important interaction by decreasing dopaminergic tone using the APTD procedure combined with anodal tDCS of the dlPFC.

2. Materials and methods

Thirty-six university students (19 females and 17 males; Mean Age = 21.7, SD= 2.4) took part. Exclusion criteria included: suffering from cardiac, hepatic, renal or neurological disorders; a history of alcohol or drug addiction; psychiatric illness; pregnancy; taking medication known to lower seizure threshold; having taken tyrosine supplements; regularly consumed more than five beverages containing caffeine per day; smoking; and having a damaged or sensitive scalp.

The study was approved by the ethics committee of Sheffield Hallam University and was conducted in compliance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (identifier: NCT03462303).

This was a double-blind, sham/placebo-controlled, randomised trial. The experimental protocol is summarised in Fig. 1A and a model of the predicted effects of the tDCS/dopamine depletion procedure is shown in Fig. 1B. The experimental session consisted of one of four conditions: tyrosine depletion plus anodal tDCS (n=9), tyrosine depletion plus sham tDCS (n=9), balanced plus anodal tDCS (n=9), and balanced plus sham tDCS (n=9). The sample size was determined using G*Power 3.1 with a power level of 80% based on mixed-design ANOVA analyses (4 groups, 4 repeated measurements [2 blocks] x [time; pre-drug/tDCS and post-drug/tDCS]) and a

large effect size of 0.14 (partial eta squared). We chose a large effect size based on previous findings from our lab using similar parameters (i.e. tDCS and drugs) and measures (i.e. cognitive flexibility) [23].

Cognitive flexibility was measured by task switching and reversal learning using the Psychology Experiment Building Language (PEBL) test battery [24] as used in previous studies by our research group [25, 26]. The APTD procedure consisted of a depletion mixture which contained 90 g of amino acids without tyrosine and phenylalanine (depleted condition) as used in previous studies [27-30]. The balanced mixture (control) also contained tyrosine and phenylalanine (balanced condition). Both the depleted and balanced mixtures had equivalent metabolic energy content (480 and 487 kcal, respectively).

tDCS over the dlPFC was applied using a DC Stimulator Plus (neuroConn, Germany) with two 5 cm x 7 cm rubber electrodes. The anode was positioned over the left dlPFC centred on F3 in the 10-20 electroencephalography (EEG) system and the cathode was positioned on the contralateral supraorbital ridge. For anodal tDCS, a current of 1.5 mA was delivered for 20 min plus 30 s fade in/fade out period. A current of 1.5 mA was chosen based on previous reports demonstrating that 2.0 mA can compromise the blinding robustness of the tDCS procedure [31-33]. For the sham treatment, a current of 1.5 mA was faded in over 30 s and then switched off. Double-blinding was achieved using the neuroConn study mode software. At the end of the experiment, participants were asked to report whether they thought they had been administered depleted or balanced drink and anodal (active) or sham (inactive) tDCS (see supplementary materials for statistical results). An electric field simulation was performed to better understand the spread of anodal stimulation over the dlPFC (see Fig. S1).

3. Results

3.1. Anodal tDCS, and dopamine depletion modulate changes in task switching (WCST)

We first analysed changes in the proportion of perseverative errors across conditions. As in our previous study [22], we measured a change in the performance from baseline (T1) to post drug/tDCS (T2) (i.e. [T2] - [T1]). Prior to doing that, we tested for potential baseline differences between the groups. There was no significant difference in perseverative errors between the four groups at baseline (see supplementary materials). A factorial between-subjects ANOVA with drug (Placebo, ADTP) as one factor and tDCS (Anodal, Sham) as the other factor demonstrated a significant main effect of tDCS [F (1, 32) =4.81, p=0.036, η^2_p= 0.13]. This effect was driven by a decrease in perseverative errors during anodal tDCS of the dlPFC compared to sham (Fig. 1C). There was neither a main effect of drug [F (1, 32) =0.44, p=0.512, η^2_p=0.01] nor an interaction between tDCS and drug [F (1, 32) =1.20, p=0.280, η^2_p=0.03] (Fig.1D).

We then analysed changes in the response times (RT) across conditions (see supplementary materials for baseline tests). A 2x2 factorial between-subjects ANOVA demonstrated a significant main effect of drug [F (1, 32) =6.06, p=0.019, η^2_p=0.15], with dopamine depletion negatively affecting reaction times compared to placebo (Fig. 1E). There was neither a main effect of tDCS [F (1, 32) =2.12, p=0.154, η^2_p=0.06] nor an interaction between tDCS and drug [F (1, 32) =0.01, p=0.912, η^2_p=0.00] (Fig. 1F).

3.2. No significant effect on Probabilistic Reversal Learning (PRL)

We investigated changes in reversal errors and total errors across conditions. We did not find any main or significant interaction effects.

4. Discussion

The primary goal of this study was to extend our recent work [22], in which we found that combining cathodal tDCS of the dlPFC (which by itself impaired cognitive flexibility) with tyrosine administration (which by itself improved cognitive flexibility) resulted in cognitive flexibility performance on par with the control condition (sham tDCS + placebo). These results suggested that increasing dopaminergic tone could counteract the detrimental effects of inhibitory cathodal tDCS of the dlPFC. In line with these findings, here we report that combining anodal tDCS of the dlPFC (which, by itself, produced improvements in cognitive flexibility, when perseverative errors were measured) with tyrosine depletion (which, by itself, impaired cognitive flexibility, when reaction times were measured) resulted in cognitive flexibility performance similar to that of the control condition (sham tDCS + balanced) (at least for reaction times: see Fig 1F), suggesting that excitatory stimulation of the dlPFC could restore the negative effects of decreasing dopaminergic tone. Overall, these data support the dopamine inverted-U hypothesis in relation to cognitive function more generally [34], and cognitive flexibility more specifically [16, 17] and the interaction between dopamine tone and tDCS in regulating cognitive flexibility.

Acknowledgements

We would like to thank the Department of Psychology, Sociology and Politics at Sheffield Hallam University for funding this research. We also would like to thank Dr Evan Edmond (Clinical Research Fellow, The University of Oxford) for his help with the electric field simulations. CJS holds a Sir Henry Dale Fellowship funded by the Wellcome Trust and the Royal Society (102584/Z/13/Z).

Conflicts of interest:

None

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Figure 1. A. Outline of the experimental procedure. Participants were instructed to refrain from eating/drinking overnight for a minimum of 8 h prior to testing. During the experimental session, participants first completed a visual analogue scale mood questionnaire (VAS1), followed by cognitive testing (T1) with the order of presentation of the Wisconsin Card Sorting Test (WCST) and Probabilistic Reversal Learning (PRL) counterbalanced across all participants. After completing the mood and cognitive testing, either a tyrosine depletion drink or a balanced mixture was administered. At 4 h and 40 min after taking the tyrosine depletion/balanced drink, which is the approximate peak plasma depletion time [35], a second mood questionnaire was completed (VAS2) and then anodal or sham tDCS was administered for 20 min. Immediately after the tDCS, a third mood questionnaire was given (VAS3) followed by the second cognitive testing (T2). At the end of the cognitive testing, a final mood questionnaire was completed (VAS4). Participants were asked to report whether they thought they had been administered the tyrosine depletion or balanced drink together with anodal or sham tDCS. B. Model of the hypothesized non-linear relationship between anodal tDCS and tyrosine depletion on cognitive flexibility. Predictions of the effects of combinations of tyrosine depletion/balanced and sham/anodal tDCS on cognitive flexibility are highlighted.

C. Illustrating task switching results with respect to perseverative errors. Perseverative errors (measured changes from baseline) on the WCST showed a significant main effect of tDCS (sham/anodal). D. Non-significant interaction between drugs and tDCS (perseverative errors). E. Illustrating task switching results with respect to reaction times. .Reaction times on the WCST showed a significant main effect of drugs (balanced/depleted). F. Non-significant interaction between drugs and tDCS (reaction times). Error bars as SEM. * represents $p < 0.05$