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Catecholaminergic modulation of indices of cognitive flexibility: A pharmaco-tDCS study

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ABSTRACT

Background: Dopaminergic activity within the dorsolateral prefrontal cortex (dlPFC) has been implicated in the control of cognitive flexibility. Much of the evidence for a causative relationship between cognitive flexibility and dopamine has come from animal studies, whilst human data have largely been correlational.

Objective/Hypothesis:The current study examines whether changes in dopamine levels through tyrosine administration and suppression of dlPFC activity via cathodal tDCS could be causally related to cognitive flexibility as measured by task switching and reversal learning.

Methods: Using a crossover, double-blind, sham controlled, counterbalanced, randomized trial, we tested the effects of combining cathodal tDCS with tyrosine, a catecholaminergic precursor, with appropriate drug and tDCS placebo controls, on two measures of cognitive flexibility: probabilistic reversal learning, and task switching.

Results: While none of the manipulations had an effect on task switching, there was a significant main effect of cathodal tDCS and tyrosine on reversal learning. Reversal learning performance was significantly worsened by cathodal tDCS compared with sham tDCS, whilst tyrosine significantly improved performance compared with placebo. However, there was no significant tDCS × drugs interaction. Interestingly, and as predicted by our model, the combined administration of tyrosine with cathodal tDCS resulted in performance that was equivalent to the control condition (i.e. tDCS sham + placebo).

Conclusions: Our results suggest a causative role for dopamine signalling and dorsolateral prefrontal cortex activity in regulating indices of cognitive flexibility in humans.

Introduction

Cognitive flexibility, often referred to as behavioural flexibility in animal studies [1], is an essential subdomain of executive function (EF) that facilitates goal-directed behavioural adaptations in response to changing circumstances [2]. The neuronal network subserving cognitive flexibility is thought to include frontostriatal circuits, specifically involving dorsolateral/medial prefrontal cortex (dlPFC/dmPFC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), nucleus accumbens (NAC) and the dorsomedial striatum (DMS) [3–6].

Much of our understanding of the neuronal underpinnings of cognitive flexibility comes from animal studies, which have utilised a combination of lesion, pharmacological and optogenetic approaches; traditionally, human studies have largely been correlational in nature. Recently, however, human studies have begun to investigate causality, via the use of non-invasive brain stimulation, particularly transcranial direct current stimulation (tDCS). Anodal tDCS applied to the left dlPFC facilitates cognitive control (a subdomain of EF required for cognitive flexibility [7,8] and cathodal dlPFC stimulation has detrimental effects on cognitive control in a hemisphere-dependent manner: cathodal tDCS applied to the right dlPFC negatively impacts performance, whereas stimulation of the left dlPFC has no behavioural impact [9,10]. Cognitive flexibility has also been tested more directly using set-shifting/task switching tasks, but the results of these have not been entirely reproducible. Anodal tDCS to the dlPFC was shown to improve performance in

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three studies [11–13] and in a fourth study cathodal, but not anodal, stimulation improved certain aspects of cognitive flexibility (post-error slowing in the WCST) but not others (perseverative or total errors in the WCST) [14]. In two of the four studies cited [12,14], stimulation of left dLPFC was shown to be effective, whereas in the other two [11,13], the left and right hemisphere of the dlPFC contributed to different aspects of task-switching performance.

It has been hypothesised that endogenous dopaminergic activity may potentially explain these somewhat contradictory findings. The involvement of dopamine in regulating cognitive flexibility particularly in animal studies is well-documented [15]. In humans, studies in which brain dopamine levels were enhanced by the administration of the dopamine precursor tyrosine have shown that increases in dopamine are beneficial to cognitive control [16,17] and, importantly, cognitive flexibility [18].

In a series of recent studies, the effects of dlPFC tDCS on set-shifting was shown to be dependent on the Val(108/158)Met *COMT* polymorphism, known to affect individuals' dopaminergic activity. Specifically, cathodal tDCS was detrimental to task performance in subjects with low dopaminergic activity (i.e. those who were Val/Val homozygous) but had no effect in those with normal dopaminergic activity (i.e. with at least one Met allele) [19]. Anodal tDCS was detrimental to task performance in individuals with high dopaminergic activity (Met/Met homozygous), but had no effect on task performance in the Val carriers.

A parsimonious model for these results was suggested by the authors (Fig. 1A). In this framework, it was postulated that cathodal tDCS acts to *decrease* dopaminergic activity, which would have little effect on cognitive performance in the Met allele carriers but would significantly impair performance in the Val/Val group as it would reduce the level of neuronal activity below that for optimal performance. Anodal tDCS would act to *increase* activity, which would have little effect on cognitive performance in the Val/Val carriers, but would increase the level of neuronal activity beyond the optimal range in the Met carriers [20]. A recent study where endogenous dopaminergic activity was increased via tyrosine administration, showed tDCS effects on working memory that were in line with this theoretical framework [21]. It is important to note, however, that tDCS cortical excitability effects may not be directly related to dopamine. With particular reference to cathodal tDCS aftereffects (as used in the current study), the evidence points at a role of glutamate [22], with administration of NMDA antagonists blocking intracortical facilitation [23] and diminished concentration of glutamate within the stimulated area [24].

The current study examined whether increases in endogenous dopaminergic activity via tyrosine and the (presumed) suppression of these by cathodal tDCS of the dlPFC could causally be related to cognitive flexibility as measured by task switching and reversal learning. In a crossover, double-blind, sham-controlled randomized trial, we tested the single and combinatory effects of tyrosine administration and cathodal tDCS of the dlPFC. Based on the theoretical framework outlined above, we predicted that tyrosine with sham tDCS would be most beneficial to cognitive flexibility. The addition of cathodal tDCS to tyrosine would remove the behavioural improvements provided by tyrosine alone, and performance during placebo plus sham tDCS would be similar to that in the tyrosine plus cathodal tDCS condition. Finally, we predicted that performance would be at its worst during placebo and cathodal tDCS condition.

Materials and methods

Participants

Twenty-four university students took part in the study (M = 20.8, SD = 2.2, 15 females and 9 males). The study was approved by the ethics committee of Sheffield Hallam University and complied with the Declaration of Helsinki. The study is registered in ClinicTrials.gov (identifier: NCT03068884). Sample size was determined using G*Power 3.1 to obtain a power level of 80% based on repeated measures ANOVA analyses (1 group, 4 measurements) with a large effect size of 0.14 (partial eta squared) and p value at 0.05. Exclusion criteria included: those suffering from cardiac, hepatic, renal and neurological disorders and individuals

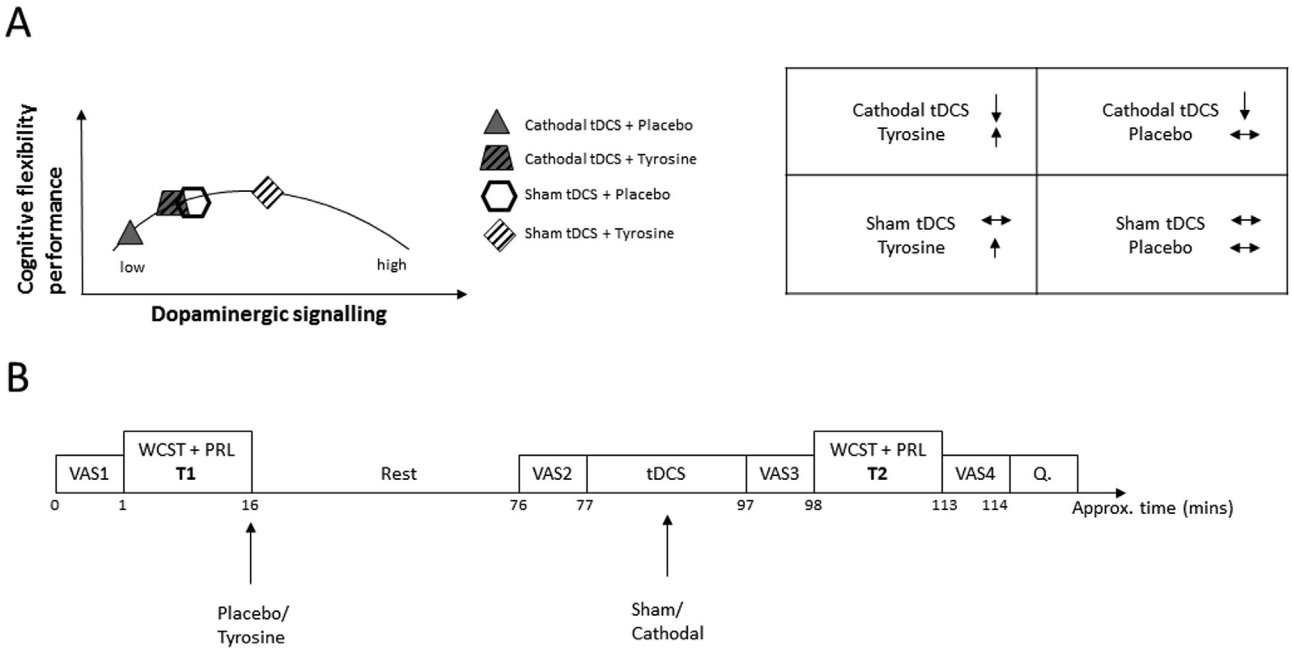

Fig. 1. A. Model of the hypothesised non-linear relationship between cathodal tDCS and tyrosine on cognitive flexibility. Predictions of effects that the combination of tDCS sham/cathodal and placebo/tyrosine will have on cognitive flexibility are also highlighted. The direction of the arrows indicate whether these manipulations are hypothesised to improve performance (up), leave it unchanged (double arrow), or impair it (down). B. Outline of the experimental procedure for each session.

with a history of alcohol or drug addiction (including nicotine), or psychiatric illness. Participants were excluded if they were pregnant, were taking medications known to lower seizure threshold, or reported having taken tyrosine supplements.

Experimental design and procedure

The experimental protocol is summarised in Fig. 1B. Briefly, this was a double-blind, crossover, sham/placebo-controlled, randomized trial with counterbalancing of conditions. Participants were required to attend four experimental sessions each lasting approximately 120 min for a total financial reward of £50. The four experimental sessions (conditions) consisted of: tyrosine plus cathodal tDCS; tyrosine plus tDCS sham; placebo plus cathodal tDCS; and placebo plus tDCS sham. A Latin square design was adopted to allocate condition order. To avoid potential carryover effects of either tyrosine and/or tDCS, each session was separated by at least 72 h.

After screening for eligibility, participants were instructed to refrain from eating/drinking overnight for a minimum of 8 h prior to testing. In each experimental session, participants first completed the mood questionnaire (VAS) (VAS1). This was followed by cognitive testing (T1) with the order of presentation of the WCST and PRL being counterbalanced for each participant in each session. The same cognitive tasks were presented across experimental sessions, sequentially. After completing mood and cognitive testing, either tyrosine or placebo was given. Sixty minutes after tyrosine/placebo intake, a second VAS was completed (VAS2), and cathodal or sham tDCS was administered for 20 min.

The choice of 1 h wait prior to tDCS was based on the finding that peak plasma concentration for tyrosine occur approximately after this period [25]. Immediately after tDCS, a third VAS was given (VAS3), and cognitive testing began (T2). At the end of the second cognitive testing, a final VAS was completed (VAS4), and participants were asked to report whether they thought that tyrosine/placebo and cathodal tDCS/sham had been administered. Participants took an average of 15 min to complete the cognitive tasks (see Fig. 1B) with some individuals taking close to 20 min. After effects of cathodal tDCS have been demonstrated to last for up to 1 h both when measured using motor evoked potentials [26–28] and brain perfusion changes [29].

Cognitive measures

Task switching and reversal learning were measured using the Psychology Experiment Building Language (PEBL) test battery [30]. Task switching was assessed using an adaptation of the Wisconsin Card Sorting Test (WCST) [31,32]. The dependent measure was the total number of errors (regardless of whether these were perseverative or not). To assess reversal learning, we used the probabilistic reversal learning (PRL) paradigm developed by Cools et al. [4]. Here, using trial-and-error feedback, participants need to discover which of two patterns is correct. To complete the PRL, participants had to complete four blocks of trials, and 40 reversals. We took mean errors per reversal as the dependent measure of interest (this is also equivalent to total number of errors if one multiplies mean errors per reversal by 40). In both WCST and PRL, participants were given practice trials before testing began and subjects were asked to respond as quickly and accurately as possible.

Drug administration

Participants received either 2.0 g of L-Tyrosine (supplied by BulkPowders Ltd.) or 2.0 g of the placebo microcrystalline cellulose (Sigma-Aldrich Co. LLC). This dosage has been shown to modulate a number of cognitive domains including deep thinking, working memory, cognitive control, and cognitive flexibility [16–18,25,33–35]. Both Tyrosine and placebo were dissolved in 400 ml of orange juice as per previously published protocols [16,25].

Transcranial direct current stimulation

A DC Stimulator Plus (neuroConn, Germany) with two 5 cm × 7 cm rubber electrodes, encased in saline soaked sponges was used. The cathode was positioned over the left dlPFC, centered on F3 in the 10–20 electroencephalography (EEG) system, while the anode on the contralateral supraorbital ridge (Fp2). Current was delivered at 1.5 mA for 20 min plus 30 s fade in/fade out periods. 1.5 mA was chosen based on previous reports which demonstrate that current at 2.0 mA can compromise the blinding robustness of the tDCS procedure [36–38]. For sham stimulation, the current was faded in over 30 s, ran for 1.5 mA and then switched off. Double-blinding was achieved using the neuroConn study mode software.

Measurement of alertness and mood

The potential influence of mood and alertness on cognitive flexibility was measured using a computerized adaptation of commonly administered visual analog scales (VAS) run in PEBL. Seven dimensions of mood/alertness were, recorded with a total minimum score of 7 (low mood/alertness) and a maximum total score of 147 (high mood/alertness).

At the end of each experimental session participants were asked to report whether they thought that active (i.e. cathodal) or sham tDCS had been delivered, and whether tyrosine or placebo (i.e. cellulose) had been administered.

Statistical analysis

Statistical analyses were performed using SPSS version 23 (SPSS Inc). The two dependent measures for cognitive flexibility were mean errors per reversal for the PRL and total number of errors for the WCST. We first used a one-way repeated measure ANOVA with one factor of condition ([cathodal tDCS + tyrosine], [sham tDCS + tyrosine], [cathodal tDCS + placebo], [sham tDCS + placebo]) to test whether there were performance differences at baseline (i.e. pre-drug/tDCS). If no significant differences at baseline were noted for both dependent measures, we calculated a percentage change at time 2 (post-drug/tDCS) compared with time 1 (pre-drug/tDCS). We then run 2 × 2 repeated factorial ANOVAs with one factor, tDCS (2 levels: sham, cathodal), and the second factor drugs (2 levels: placebo, tyrosine) to test for main effects (tDCS, drugs) and interactions.

Mood data were analysed using a two-way factorial repeated measures ANOVA, where the factor of Time had four levels (VAS 1–4), with Bonferroni post-hoc corrections applied.

The double blinding efficacy of tyrosine/placebo and cathodal tDCS/sham was analysed using a percentage correct measure. A score of 1 was given if a participant correctly identified condition whereas a score of 0 if not. We investigated the combined effects of drug (tyrosine/placebo) plus tDCS stimulation (cathodal/sham) on accuracy rates. Here chance level was 25% and a Cochran's Q test for dichotomous data was used to investigate significance. In all tests, a p value of <0.05 was considered significant.

Results

Putative dopamine increases and cathodal tDCS lead to changes in probabilistic reversal learning (PRL)

A one-way repeated measures ANOVA with one factor of Condition demonstrated no significant difference in performance at

baseline (i.e. pre-drug & tDCS; Time 1) between sessions [F (2.00, 46.19) = 2.37, p = 0.104]. We therefore calculated percentage change in mean errors per reversal at time 2 compared with time 1. A 2 × 2 factorial repeated measures ANOVA demonstrated a significant main effect of tDCS [F (1, 23) = 5.37, $p = 0.030$, $_{\eta}p^2 = 0.19$], with cathodal tDCS of the dlPFC negatively affecting performance compared to sham (Fig. 2A). We also report a significant main effect of drugs [F (1, 23) = 5.98, $p = 0.023$, $_{\eta}p^2 = 0.20$], with tyrosine administration positively affect performance compared to placebo (Fig. 2B). There was no significant tDCS × drug interaction [F (1, 23) = 0.12, $p = 0.729$, $_{\eta}p^2 = 0.00$].

To check for potential practice/ceiling effects of PRL testing, we compared reversal errors during pre-drug/tDCS across the 4 sessions. We found that amount of practice did not produce a significant change in reversal errors [F (3, 69) = 1.02, $p = 0.386$].

No significant effect on Wisconsin Card Sorting Test (WCST)

The primary dependent measure of interest in the WCST was total number of errors. As with the PRL, there was no difference in errors at time 1 across the sessions [F (2.21, 51.00) = 1.67, p = 0.181]. We therefore calculated percentage change in total errors at Time 2 compared with time 1. A 2 × 2 factorial repeated measures ANOVA revealed no main effect of tDCS [F (1, 23) = 0.01, $p = 0.900$, $_{\eta}p^2 = 0.00$] (Fig. 3A), nor a main effect of drugs [F (1, 23) = 0.90, $p = 0.352$, $_{\eta}p^2 = 0.03$] (Fig. 3B) nor a tDCS × drugs interaction [F (1, 23) = 0.47, $p = 0.498$, $_{\eta}p^2 = 0.02$].

Non-condition-dependent increase in mood and alertness during session

Results from the VAS are summarised in the Supplementary Material Table S1. There was no significant main effect of Condition on mood [F (1.79, 41.20) = 1.05, $p = 0.374$]. However, there was a significant main effect of Time [F (2.23, 51.42) = 7.19, $p = 0.001$, $\eta^2_p = 0.23$]. Bonferroni-adjusted *post hoc* t-tests revealed that mood significantly improved from VAS 1 (baseline) (M = 99.7, SD=20.1) to VAS 3 (post-drug/tDCS) (M=108, SD=17.8) ($p = 0.006$) and from VAS 2 (post-drug) (M=103.5, SD=17.5) to VAS 3 (post-drug/tDCS) ($p = 0.002$), but not between VAS 1 and VAS 2 ($p = 0.508$), VAS 1 and VAS 4 (M=105.5, SD=19.6) ($p = 0.085$), VAS 2 and VAS 4 ($p = 1.00$) and VAS 3 and VAS 4 ($p = 0.652$). There was no significant interaction between Condition and Time [F (4.46, 102.78) = 0.97, $p = 0.887$], indicating that improvement in mood occurred independent of Condition.

Effective participant-blinding across sessions

We analysed the probability of a subject correctly identifying which condition they had received in any given session. Mean accuracy rate across conditions was at chance at 25%. Cochran's Q test determined that there was no statistically significant difference in the proportion of participants accurately guessing their condition, X^2 (3) = 5.455, $p = 0.141$, confirming the efficacy of the blinding across sessions.

Discussion

The aim of this study was to investigate the role of catecholaminergic modulation in cognitive flexibility, and whether this role could be modulated by tDCS inhibition of the dlPFC. We found an effect on one sub-domain of cognitive flexibility, namely, reversal learning but not task-switching. Our finding that cathodal tDCS impacts reversal learning but not task-switching therefore suggests that these two subdomains of cognitive flexibility may be controlled by a differential neuronal network. Although the dlPFC seems to be involved in both reversal learning and WCST [4,39], there appears to be a differentiation with respect to the subcortical regions that contribute to the execution of these tasks [3,40]. It may be, therefore, that dlPFC tDCS differentially affects these anatomically distant subcortical regions [29,41,42].

As predicted by our model, performance on the [cathodal tDCS + placebo] condition was worst, with [sham tDCS + placebo] and [cathodal tDCS + tyrosine] second, and [sham tDCS + tyrosine] best. The absence of a statistically significant interaction between tDCS (sham, cathodal) and drugs (placebo, tyrosine) is not unexpected and predicted from our model (Fig. 1A). In that, the only comparison hypothesised to significantly differ was the [cathodal tDCS + placebo] condition with the [sham tDCS + tyrosine]. Nevertheless, there remain a number of open questions as to the physiological mechanisms that resulted in these effects. In the following section, we will attempt to provide some potential explanations.

The detrimental effects of cathodal tDCS applied to dlPFC on specific aspects of cognitive flexibility (i.e. reversal learning) but not others (i.e. task switching) are in line with some previous findings [9,10], but not entirely with others [14]. Methodological differences between studies including disparate measures of cognitive flexibility being used, on-line versus offline stimulation, left or right hemisphere targeting, size of the stimulating electrode, position of the reference electrode, the employment of between subjects versus crossover designs, duration of stimulation, means

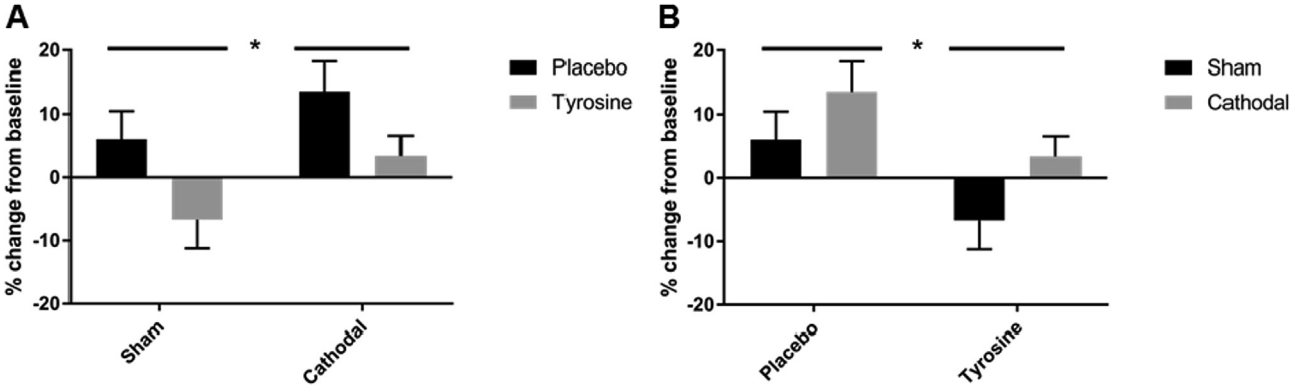

Fig. 2. A. Probabilistic reversal learning (PRL) performance (reversal errors) expressed as a percentage change from baseline (i.e. PRL performance at time 1 [pre-drug/tDCS], vs time 2 [post-drug/tDCS]). There was a significant main effect of tDCS. B. As for A but showing the main significant effect of drugs. Note, there was no significant tDCS × drug interaction. Error bars as standard error of the mean (SEM). * represents $p < 0.05$.

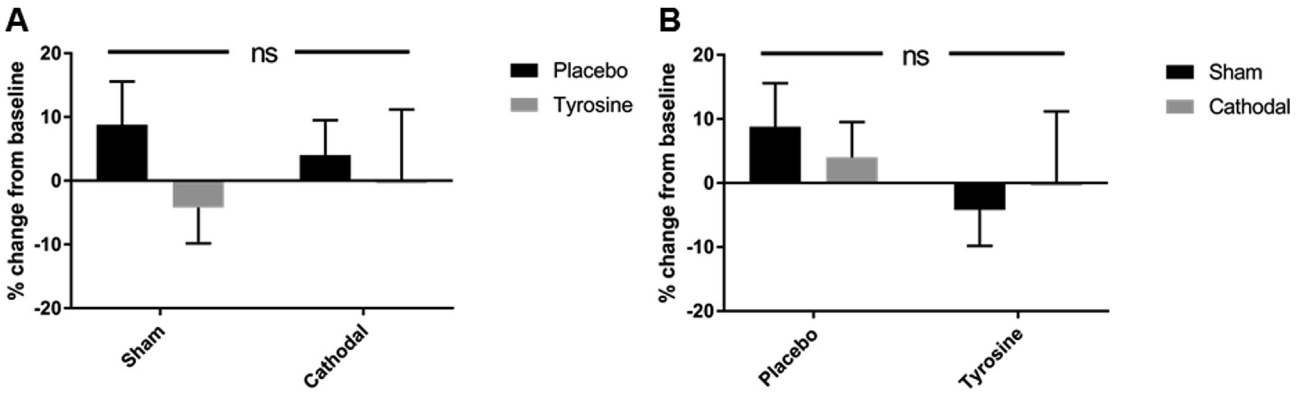

Fig. 3. A and B. Wisconsin Card Sorting Test (WCST) performance (total errors) expresses as a percentage change from baseline (i.e. WCST performance at time 1 [pre-drug/tDCS] vs time 2 [post-drug/tDCS]. There was neither a main significant effect of tDCS (A) nor a main significant effect of drugs (B). Note, there was no significant tDCS × drug interaction. Error bars as standard error of the mean (SEM). ns = not significant.

that comparisons should be made with caution. Several reviews have evaluated the influence of these methodological variables on the reproducibility of tDCS findings [43–45]. We cannot, for example, categorically exclude the influence of the reference/return electrode on cognitive flexibility performance, as the reference electrode can have differential physiological effects depending on whether this is placed over another cranial area or in extracranial regions [46,47]. This is an issue that relates more generally, to tDCS spatial resolution as modelling studies demonstrate that the target/active electrode elicits peak electrical fields that are 2–4 cm away from the electrode [48–50].

The primary goal of this research was to understand the modulation of dopaminergic agents on tDCS effects whilst acknowledging the contribution that other factors play to affecting tDCS results.

The observation that (cathodal tDCS + placebo) and (sham tDCS + tyrosine) were at opposite ends of reversal learning performance may relate to different mechanisms. First, the negative effects on performance were specific to the inhibition of activity of dlPFC neurons. This inhibition may have a dopaminergic component as highlighted by previous reports on dopamine polymorphisms and cathodal dlPFC [19,20]. In line with this mechanistic hypothesis, participants with low baseline dopamine levels are negatively affected by cathodal tDCS. Conversely, in participants with high COMT activity, anodal tDCS negatively impacts cognitive flexibility. This supports a long-standing view of a nonlinear inverted U-relationship between dopamine concentrations and performance. Nevertheless, the possibility that cathodal tDCS may affect other neurotransmitters, chiefly glutamate but also GABA, cannot be excluded [24,51].

Second, the positive effects on performance can be attributed to overall increases in dopamine synthesis across the brain as opposed to being specific to the dlPFC. Whilst both tyrosine (alone) and anodal dlPFC (alone) have been reported to improve cognitive flexibility [11–13,18], it is plausible that these improvements are the result of different neurobiological mechanisms.

A particular goal of this investigation was to test the hypothesis that the combined administration of tyrosine with cathodal dlPFC could in effect, render performance indiscernible from that of the control condition [tDCS sham + placebo]. The data support our original hypothesis. This, at least behaviourally, points at tyrosine (and indirectly dopamine) modulating tDCS effects on reversal learning, as shown by a recent report looking at working memory [35].

Physiologically, the effect of tyrosine on cortical excitability combined with cathodal tDCS would need to be confirmed. Previous studies have shown that the dopamine precursor L-DOPA eliminated the expected decrease in cortical excitability observed after cathodal tDCS at low and high doses [52], but this effect was dose-dependent: a medium dose had no effect [52,53].

Although both tyrosine and L-DOPA are dopamine precursors, the conversion of the tyrosine into dopamine is restricted, both by competition from other endogenous amino acids and by the rate-limiting tyrosine-hydroxylase enzyme, meaning that tyrosine administration does not lead to greatly elevated concentrations of dopamine [54]. Conversion of L-DOPA into dopamine, on the other hand, is not influenced by the above factors. It is plausible, therefore, that effects on dopamine levels of the tyrosine in our study was equivalent to administering a low dose of L-DOPA.

However, it is worth emphasizing that there are no published data comparing the bioequivalence of tyrosine dosage to L-dopa, thus future studies would need to establish this.

Conclusion

We provide preliminary behavioural evidence that dopaminergic administration modulates tDCS effects on cognitive flexibility. Our findings contribute to an expanding literature which aims to uncover factors that underlie the known inter-subject variability of this technique. Future investigations that manipulate tyrosine availability such as the acute tyrosine/phenylalanine depletion procedure [55,56] combined with tDCS would aid our understanding of the relationship between the inverted U-relationship between dopamine concentrations, performance and tDCS polarity.

Conflicts of interest

None.

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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.2018.12.001.

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