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Dietary tyrosine consumption modulates the effects of tDCS, but not tRNS, on planning behaviour

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Transcranial Direct Current Stimulation (tDCS) holds great promise for alleviating various diseases and enhancing cognitive function. Despite its potential, contradictory findings remain prevalent in the field due to a combination of methodological [1] and interindividual factors. A decade of diverse research methodologies has consistently shown that variations in dopaminergic (DA) activity, specifically within the realm of executive function (EF), can predict the direction of tDCS effects on EF [2–5].

Our study aimed to elucidate the impact of the DA precursor, tyrosine, on tDCS-induced effects on EF performance. Previous studies conducted by our research group demonstrated that both pharmacological depletion and augmentation of tyrosine affected tDCS polarity, resulting in either restoration or impairment of EF [2,3]. Although these studies have been instrumental in revealing a causative link between putative DA activity and EF, the findings were primarily based on acute, short-term changes in DA function. Hence, our first objective in this study was to ascertain whether monthly dietary consumption of tyrosine-rich foods similarly modulate the effects of tDCS on EF. Our second objective was to compare the effectiveness of transcranial random noise stimulation (tRNS), which is a non-invasive brain stimulation technique that can also alter cortical activity. Compared to tDCS, tRNS is polarity-independent, has a wider neuromodulating influence, and is less affected by cortical folding [6]. However, the neurophysiological mechanisms of tRNS are less understood, and it remains to be explored whether tRNS influences EF through DA-related pathways.

We conducted a double-blind, crossover, sham-controlled, counterbalanced, randomised trial (registered at ANZCT, identification number: ACTRN 12623000351617). Thirty healthy participants were administered active tDCS (1.5 mA for 20 minutes), active tRNS (3 mA peak-to-peak; 100–640 Hz), or Sham stimulation (1.5 mA faded in for 30 seconds, then off) of the bilateral dorsolateral prefrontal cortex (dlPFC) over three experimental sessions while completing two tasks measuring aspects of EF. The Tower of London (TOL) test was used to measure planning and the Corsi Block-Tapping (Corsi) task was used to measure working memory. Based on the 10–20 electroencephalography (EEG) system, the anode was placed on F3 and the cathode was placed on F4 of the dlPFC. Participants completed the two tasks a total of six times: pre-sham, pre-tDCS, pre-tRNS, sham, active tDCS, and active tRNS (i.e., online sham/tDCS/tRNS; see Fig. 1 in the Supplementary Materials for more details). The measures of interest included the total number of moves taken and time spent on the TOL test, and the memory span and reaction times on the Corsi task. The high and low tyrosine groups were classified using a median split approach, as in our previous publications [4,5], which adopted a validated Dietary screener questionnaire to measure tyrosine consumption [7]. The questionnaire, which participants completed once during the first experimental session, inquired about foods consumed over the past month. The groupings were entered into a series of 2 x (3 x 2) factorial mixed-design ANOVA (see Supplementary Materials 1.1–1.9 for more details).

Here, we report the key findings of the study (see Supplementary Materials 1.7–8 for additional results). There was a significant Tyrosine × Brain Stimulation × Time interaction for the total number of moves in the TOL test [F (2, 56) = 3.71, p = 0.031, η_p^2 = 0.117]. This three-way interaction was further analysed by breaking down the Brain Stimulation × Time for high and low tyrosine groups separately. There was a significant two-way interaction effect in the low tyrosine group [F (2, 28) = 4.01, p = 0.029, η_p^2 = .223], but not in the high tyrosine group. These results were further investigated by simple main effects. The total number of moves was significantly lower (i.e., improved planning performance) during active tDCS compared with pre-tDCS (p = 0.002), but there was no statistical reduction in the total number of moves with sham (p = 0.985), or more interestingly, with the tRNS conditions (p=.630). Furthermore, online tDCS produced a significant reduction in the total moves compared to both sham (p=.010) and tRNS (p = 0.005). Planned contrasts showed that planning performance was better in those who received online tDCS in the low tyrosine group compared to the high tyrosine group (p = 0.012) (see Fig. 1 for complete results). There were no significant three-way interactions for the time taken in the TOL test or for working memory performance in the Corsi task.

Overall, we found that tDCS effects on planning performance, but not working memory, could be explained by variations in the daily intake of tyrosine-rich foods. Specifically, only participants in the low tyrosine

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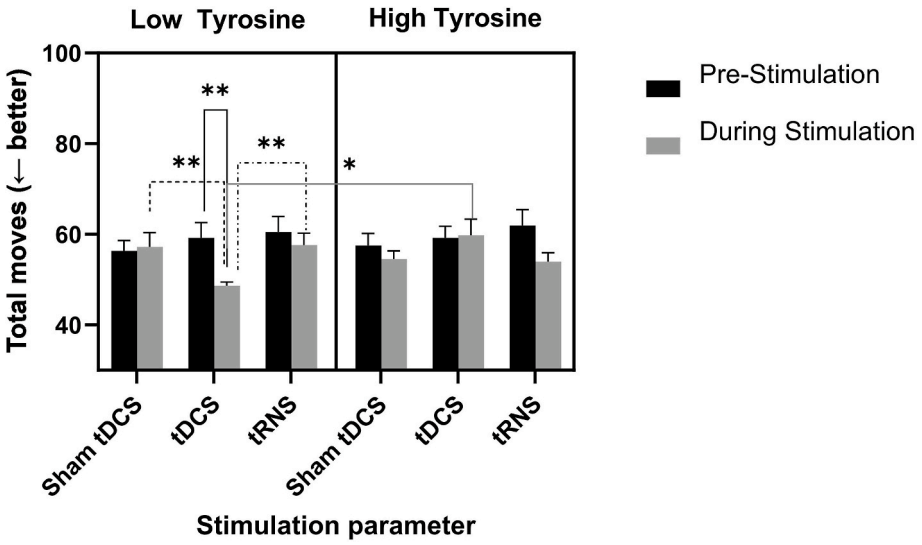

Fig. 1. A significant three-way interaction effect (Brain Stimulation × Time × Tyrosine) was observed for the total number of moves in the Tower of London task. This interaction was further analysed through two-way factorial ANOVA (Brain Stimulation × Time) stratified by high and low tyrosine levels. Post-hoc analyses included examination of the simple main effects and planned contrasts. The low tyrosine group showed significantly lower total number of moves (indicating better planning performance) during online tDCS compared to pre-tDCS. Additionally, total moves during tDCS were significantly lower compared to both Sham and tRNS conditions. Planned contrasts further revealed a significant decrease in the total moves during tDCS in the low tyrosine group compared to the high tyrosine group. Error bars represent standard error of the mean (SEM). Asterisks denote significance levels (*p ≤ .05, **p ≤ .01). The data are displayed using the raw format because it is easier to interpret. However, note that the inferential statistics were conducted using a reciprocal of the cube to improve normality, as given by the following formula: $f(x) = \frac{1}{x^3}$.

group benefited from tDCS. Interestingly, this finding was not replicated with tRNS.

These results support previous research that demonstrated an association between habitual dietary tyrosine intake and cognitive performance, particularly for EF [8]. Importantly, the current study extends the findings in our previous investigations that showed *acute* tyrosine augmentation or depletion interacted with tDCS to modulate EF performance [2,3]. Furthermore, the simple but elegant method of classifying participants with putative low and high levels of DA using a median split approach, as in our two recent publications [4,5], could be a useful analytical strategy to predict the efficacy of tDCS on EF. This was supported by additional analyses (see Section 1.8 of the Supplementary file). The most parsimonious mechanistic explanation of the interaction between DA concentration and tDCS is that the polarity-dependent changes in cortical excitability induced by tDCS are altered by DA activity, as exemplified in studies where the DA precursor $_{L}$-DOPA was administered during tDCS [9,10]. Critically, cortical excitability changes in these studies were non-linear and dosage dependent. In turn, cognitive performance and DA levels have been theorised to reflect an inverted-U-shaped dose-response curve, whereby too little and too much DA negatively impacts performance [11], which would offer a plausible, albeit not fully conclusive, explanation for the interactive effects between tDCS and DA on EF.

Finally, in our investigation, the application of tRNS resulted in planning performance that was equivalent to sham and was not modulated by tyrosine levels. We speculate that as tRNS is polarity-independent [6], DA activity here only plays a minor role on EF, although this hypothesis needs to be confirmed. Given the current study relies on a putative marker of DA, future investigations are needed to refine our existing understanding of the tDCS-DA-EF relationship by using techniques such as Liquid Chromatography-Mass Spectrometry to determine urinary DA metabolite concentrations more precisely.

CRediT authorship contribution statement

Oliver Buck: Writing – review & editing, Investigation. **Tenielle Found:** Writing – review & editing, Investigation. **Rachel Weldon:** Writing – review & editing, Investigation. **Lee Wei Lim:** Writing – review & editing, Writing – original draft, Formal analysis. **Luca Aquili:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2024.04.014.

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