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Routine behaviour, a putative dopamine marker, predicts cognitive flexibility by tDCS of the dlPFC☆

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A large body of accumulating evidence shows that alterations in the dopaminergic (DA) system, either endogenous or exogenous, can modulate the effects of transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (dlPFC) on reinforcement learning (RL) and cognitive flexibility (CF) tasks. This has been demonstrated using a variety of methodological approaches, including pharmacological, genetic, physiological, and self-reported measures of personality, although the latter relates to the assessment of impulsivity rather than RL or CF [1–5].

Recently, Ersche et al. developed a self-reported questionnaire to measure automatic and routine behaviors called the Creature of Habit Scale (COHS) [6,7]. The development of habits from a neuroscience perspective is believed to involve different regions in the DA pathway. The regions of DA involvement vary depending on whether habit formation is in its early stages when behaviour is goal-orientated and thus a key feature of optimal RL and CF performance (ventral-medial striatum), or in its later stages when behaviour is more automatic and less goal-orientated (dorsal-lateral striatum) [8]. Therefore, routine behaviour as assessed by the COHS, could potentially act as a putative psychological marker of DA activation along the ventral to dorsal regions during habit formation.

To test the sensitivity of COHS, we combined COHS with tDCS of the dlPFC while participants completed the Wisconsin Card Sorting Task (WCST) to assess CF. Given that habitual behaviour is associated with deficits in CF [9] and that high scores in COHS routine are associated with high impulsiveness [7], which in turns predicts poor CF [10], we hypothesized that low/high COHS routine scores may mediate the directional effects of tDCS.

We conducted a double-blind, crossover, sham-controlled randomized trial (registered at ANZCT, identification number: ACTRN12622000871741) on 30 healthy participants. We administered active tDCS (1.5 mA for 20 minutes) or Sham tDCS (1.5 mA faded in for 30 seconds, then off) of the dlPFC over two experimental sessions while participants performed the WCST. The positioning of the electrodes consisted of the F3 electrode as the cathode and the Fp2 electrode as the anode according to the 10–20 electroencephalography (EEG) system. The WCST was administered four times, before and during sham and active tDCS sessions (online tDCS group: first 10 minutes tDCS ON and last 10 minutes tDCS ON while participants completed the WCST; see Fig. 1A for a summary of the procedure). The measures of interest included total errors and perseverative errors. We used a median split approach [5] to classify those with high and low automatic and routine behaviors as measured by COHS. The groupings were then entered in a series of 2*(2*2) factorial mixed design ANOVA (see Supplementary Materials 1.1–1.7 for detailed information).

Here, we report the key findings of the study (see Supplementary Materials 1.7 for additional results). There was a significant Routine*tDCS*Time interaction for total errors [F (1, 28) = 6.05, p = .020, η^2_p = .178]. This three-way interaction was analysed by breaking down the tDCS*Time for high and low routine groups separately. There was a significant two-way interaction effect in the low routine group [F (1, 14) = 3.29, p = .047, η^2_p = .253], but no observed effect in the high routine group (Fig. 1B). These results were further investigated by simple main effects. Total errors were significantly lower (i.e., an improvement in CF) during active tDCS compared with pre-tDCS (p < .001), and importantly, there was no statistical reduction in the total errors in the sham condition (p = .095) (Fig. 1C). There were no significant three-way interactions in perseverative errors for Routine and no significant three-way interactions for Automaticity (see Supplementary Materials 1.7 for exploratory analyses).

Overall, we found that those with high and low routine behaviors responded differently to tDCS stimulation with respect to CF total errors as measured by the WCST. Specifically, there was an improvement in the low routine group (i.e., lower total errors, indicating better CF) during active tDCS compared with pre-tDCS. In contrast, the same CF improvement was not seen in the high routine group or in the sham condition. Our work expands on the findings from a recent investigation that found an association between personality traits and preferential effects of tDCS on performance [4]. Importantly, the results of our study support evidence from pharmacological, genetic, and physiological studies that DA is a likely modulator of the effects of tDCS on RL and CF [1–3,5]. However, unlike previous findings that showed a dose-dependent

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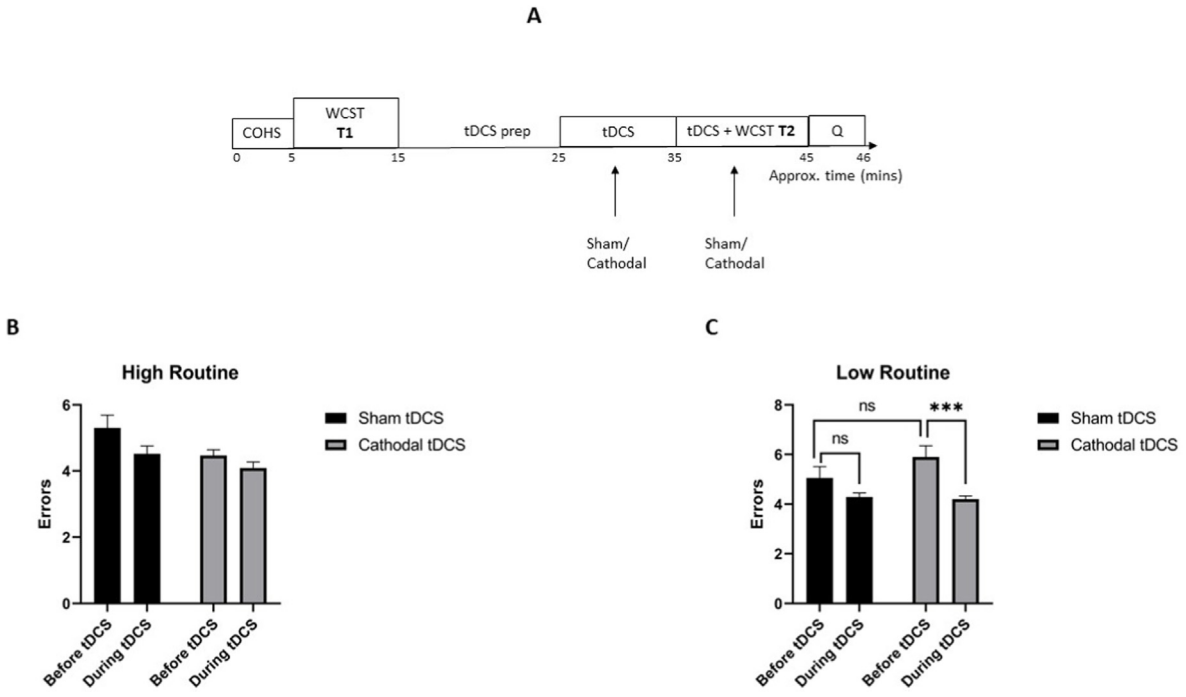

Fig. 1. A. Outline of the experimental procedures. This crossover randomized trial consisted of two testing sessions, each separated by a minimum of 72 hours. Participants were asked to refrain from eating and drinking for a minimum of 3 hours prior to testing. During the experimental session, participants first completed the COHS, followed by WCST to assess cognitive flexibility (T1). Next, active tDCS or sham tDCS was delivered for 10 minutes while participants were inactive, followed by another 10 minutes while performing the cognitive flexibility test (T2). Participants completed a questionnaire asking them to report whether they thought they had received sham or active tDCS. COHS=Creature of Habit Scale; WCST= Wisconsin Card Sorting Test; T1/T2 = Time 1/Time 2. tDCS prep = tDCS preparation; Q = Double-blind questionnaire. Numbers under the horizontal line represent approximate time (in minutes) of events. **B.** Three-way significant interaction effect (Routine*tDCS*Time) for total errors was broken down into two-way factorial ANOVAs (tDCS*time) split by high and low Routine. There was a non-significant interaction between Time*tDCS for total errors in the high routine group. **C.** There was a significant interaction between Time*tDCS for total errors in the low routine group, which was further investigated by simple main effects. Total errors were significantly lower during active tDCS compared to before tDCS. During tDCS = Online tDCS. Error bars as SEM. *** represents $p < .001$. ns = non-statistically significant.

relationship between DA and tDCS on RL and CF performance, we found the putative DA activity captured by COHS suggests tDCS affects the DA neuronal pathways, as represented by low (ventral-medial striatum DA pathway) and high (dorsal-lateral striatum DA pathway) levels of routine-like behaviors.

Our findings show that those with low routine behaviors benefited from tDCS of the dlPFC, which tends to have an impairing effect on RL and CF based on the previous literature (when the cathode is placed on F3), although this needs to be further explored in a series of mechanistic investigations. Nevertheless, one of the primary goals of tDCS research is to provide more consistent and replicable results. One way to achieve this is to better understand the sources of heterogeneity among individuals that drive variability of outcomes. In addition to the (putative) differential involvement of DA pathways on routine-like behaviors measured by COHS in this study, other factors have been reported to modulate the direction and effectiveness of tDCS of the dlPFC on RL and CF tasks, including polymorphisms in DA genes (COMT) [3], increased DA concentrations by administration of the precursor tyrosine [2], decreased DA by depletion of tyrosine and phenylalanine [1], and striatal DA activity as measured by eyeblink rate [5]. Therefore, we believe the aforementioned literature can provide the groundwork for further investigations into the mechanistic nature of our findings.

Author contributions

LA designed the study. GY performed the research. LA and GY analysed the data. GY, LWL, and LA wrote the manuscript.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from.

Declaration of competing 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.2023.01.1676.

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