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Investigating the effects of transcranial direct current stimulation on obstacle negotiation performance in Parkinson disease with freezing of gait: A pilot study

To the editor

Freezing of gait (FOG) is a severe symptom associated with Parkinson's disease (PD) which often occurs during complex walking, such as stepping over an obstacle in the ground, or while performing a secondary task [1]. To date, FOG poorly responds to pharmacological interventions and hardly affects daily life activities, thus the development of innovative treatments is needed. In this context, transcranial direct current stimulation (tDCS) has been studied as a non-pharmacological option [2–4]. Indeed, multiple sessions of tDCS over M1 were able to decrease number and duration of FOG episodes [4]. Later, multi-target tDCS stimulation over the dorsolateral prefrontal cortex (DLPFC) plus M1 showed greater effect on FOG compared with tDCS targeting M1 alone [2]. With respect to dual-task gait, we have demonstrated that one session of ANODAL tDCS over the left-DLPFC improved spatiotemporal gait parameters in PD subjects with FOG when required to accomplish a cognitive dual-task [3]. However, the possibility to improve gait parameters when walking is combined with a secondary motor task, by applying ANODAL tDCS on DLPFC, in patients with PD with FOG, is still unexplored. We hypothesized that: (i) ANODAL tDCS would lead to greater improvement in obstacle negotiation performance than SHAM tDCS and (ii) the tDCS-induced effect would be stronger in PD subjects with FOG than patients without FOG.

We employed a double-blind, sham-controlled, within-subjects study design. The study was approved by local ethical review board and all participants gave written **informed consent** prior to inclusion. Inclusion criteria were: idiopathic PD; Hoehn and Yahr (H&Y) stage 1–2.5; walk without assistance; Mini-Mental Status Examination score > 24/30.

Twenty-one PD patients were included for this study and subdivided into two groups based on the presence of FOG according to the new FOG Questionnaire [5]: eleven participants who experienced FOG were included in the FOG + group (mean age: 69.20 ± 5.20 years) and 10 PD subjects were included in the FOG- group (mean age: 70.36 ± 6.23 years).

In two separate sessions, participants randomly received ANODAL (1.5 mA for 20 minutes) or SHAM (1.5 mA for 20 seconds) [6] tDCS targeting the left-DLPFC (Fig. 1A). Details of tDCS procedures are reported in the Supplementary Materials. The effect of tDCS stimulation on obstacle negotiation task (i.e. walking back and forth for 1 minute while crossing a shoe box, Fig. 1B) was assessed via GAITRite®. We measured: step length; stride velocity and double support time during obstacle crossing. Evaluation of gait was performed before and after both ANODAL and SHAM tDCS-sessions. PD subjects were tested in their best therapeutic condition ("ON" phase, ≈30 minutes after having taken the medication).

TDCS-induced changes on spatiotemporal parameters of gait were analysed with a Repeated Measure (RM) ANOVA, with STIMULATION (ANODAL, SHAM) and TIME (pre, post) as within subject factors and GROUP (FOG+, FOG-) as between-subject factor. Pearson's correlation coefficient was used to assess associations between changes in obstacle crossing parameters and disease duration and H&Y stage.

Participants characteristics were similar between the two groups (Supplementary Materials). No adverse tDCS-related events were noted. Statistical analysis showed a significant STIMULATION × TIME interaction for all the variables considered. Post-hoc analysis revealed that only after ANODAL tDCS step length ($p = 0.003$), stride velocity ($p < 0.001$) and double support time ($p = 0.022$) significantly improved. These changes significantly correlated with disease duration (step length: $p = 0.001$, stride velocity: $p = 0.008$) and H&Y stage (stride velocity: $p = 0.035$; double support time: $p = 0.009$). No changes were detected after SHAM stimulation. No significant STIMULATION x TIME × GROUP interaction was found, suggesting any greater improvement in FOG + group compared to FOG-group.

In this study, we assumed that ANODAL tDCS targeting the left-DLPFC would improve obstacle crossing performance in PD subjects and in particular in those with FOG. This was based on recent notions that increasing DLPFC excitability improved motor [7], cognitive [8], and dual-task performance [3] in PD subjects and reduced FOG severity [4]. Here, we demonstrated that a single session of ANODAL tDCS targeting the left-DLPFC induces similar improvements in complex gait in PD subjects with and without FOG.

To explain the lack of a greater effect of tDCS on PD FOG + respect to PD FOG-, several explanations could bring into play: (i) the type of task; (ii) the target area of the stimulation; (iii) medication state of participants. First, the obstacle itself could have acted as a visual cue, so as to alleviate instead of causing FOG episodes during dual-task gait [9]. This was partially confirmed by the fact that any FOG episode occurred in PD FOG + participants during the experimental sessions. Secondly, even if we demonstrated that the facilitation on the left-DLPFC improves cognitive dual-task gait performance in PD FOG+ [3], it has also been showed that a multitarget (M1 plus DLPFC) tDCS is able to reduce FOG

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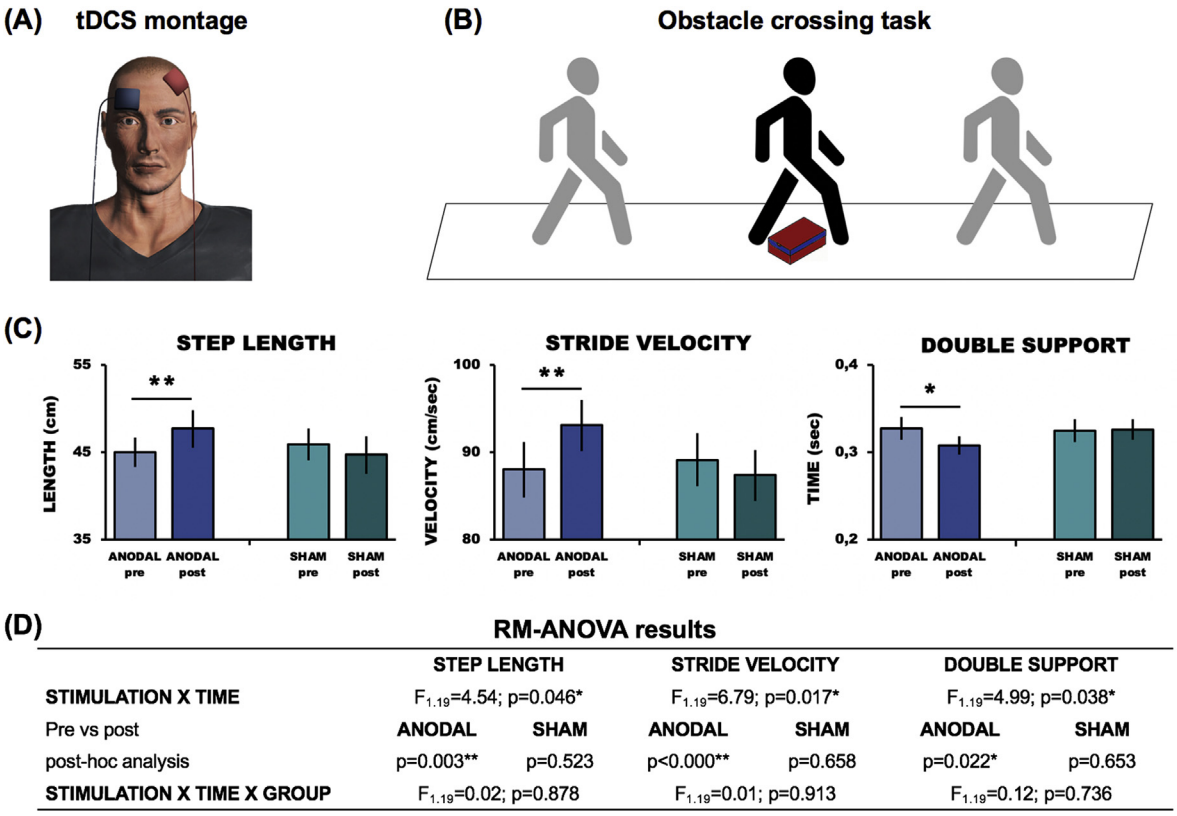

(D) RM-ANOVA results

	STEP LENGTH		STRIDE VELOCITY		DOUBLE SUPPORT	
STIMULATION X TIME	$F_{1,19}$=4.54; p=0.046*		$F_{1,19}$=6.79; p=0.017*		$F_{1,19}$=4.99; p=0.038*	
Pre vs post	**ANODAL**	**SHAM**	**ANODAL**	**SHAM**	**ANODAL**	**SHAM**
post-hoc analysis	p=0.003**	p=0.523	p<0.000**	p=0.658	p=0.022*	p=0.653
STIMULATION X TIME X GROUP	$F_{1,19}$=0.02; p=0.878		$F_{1,19}$=0.01; p=0.913		$F_{1,19}$=0.12; p=0.736	

Fig. 1. Panel (A): Illustration of tDCS montage. Red electrode depicts the anode over the left-DLPFC (F3 position). Light blue the cathode (Fp2 position). **Panel (B):** Cartoon of obstacle crossing task. **Panel (C):** TDCS-induced changes on gait parameters. Histograms show mean values for kinematic data recorded before (pre) and after (post) tDCS stimulation. Error bars indicate Standard Error (ES). Asterisks indicate statistical significant difference ($^{*}p < 0.05$; $^{**}p < 0.01$). **Panel (B):** Details of RM ANOVA interactions and statistical analysis results are reported. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

severity more than targeting M1 alone [2]. Therefore, we can hypothesize that for inducing a greater improvement on PD FOG+ a multitarget stimulation should be considered as a further option. Thirdly, here we tested the effect of tDCS while PD participants were in their best therapeutic condition ("ON" phase). Although FOG is widely "drug-resistant", it is also well known that FOG episodes occur more frequently in OFF drug condition [10] (i.e. without medication). Therefore, the expected greater effects on FOG patients might have been hidden by pharmacological induced benefit on motor symptoms.

Finally, we found that the higher was the disease duration and the H&Y stage, the greater were the improvements in spatiotemporal crossing parameters, suggesting that PD participants with a more severe clinical profile benefited more from active tDCS stimulation. These finding may be helpful in identifying clinical profile of PD subjects who will respond better to DLPFC neuromodulation, especially when thinking to design a multisession study.

Limitations of this study concern its relatively small sample size, hence results should be interpreted with caution and reproduced in a larger cohort of patients. Also, long lasting effects and tDCS-induced changes on dual-task gait in an ecological setting were not explored.

Nevertheless, these findings support that non-invasive neuromodulation could represent an adjunctive tool for novel treatment aimed at improving dual-task gait in PD patients.

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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.2019.07.006.

Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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