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Combining trauma script exposure with tDCS to alleviate symptoms of posttraumatic stress disorder: A two-arm randomized sham-controlled multicenter trial

Dear editor,

Posttraumatic stress disorder (PTSD) affects 3.9 % of the global population, with only half experiencing remission [1]. Exposure therapy for PTSD aims to act on identified dysregulated brain regions [2]. Certainly, functional alterations occur in key brain regions of the fear-processing network, including the amygdala (AMY) [3] and the ventromedial prefrontal cortex (vmPFC) [4], a top-down control region engaged in extinction. Furthermore, the left dorsolateral PFC (dlPFC), known for cognitive control and emotion appraisal, is implicated in top-down control of the vmPFC [4] and in intrusive traumatic memories [5]. Moreover, stimulating this region could help with comorbid depressive symptoms. Combining exposure therapy with a neuromodulatory technique targeting the dlPFC is a logical proposition based on our understanding of PTSD-induced brain alterations, posttraumatic and comorbid depressive disorders. The integration of transcranial direct current stimulation (tDCS) into therapeutic practices, with its advantages of patient tolerance, cost-effectiveness, and easiness of availability, should be further explored. The technique involves applying a mild direct electrical current across the scalp, flowing electrons from an anode to a cathode. Consequently, our study aimed to explore whether multiple sessions of anodal tDCS over the left dlPFC during trauma exposures could diminish PTSD-related symptoms (Fig. 1A and B), and achieve beneficial effects in a shorter timeframe.

Our study was a superiority randomized controlled trial involving five university hospital centers. All actors of the trial were kept blinded of treatment groups for study duration. Sixty-three participants (18–65 years old) suffering from chronic PTSD (3 months–10 years), were recruited and allocated in a 1:1 ratio between two groups. The diagnosis of PTSD was established by a psychiatrist according to the DSM-5, confirmed by the Clinician Administration PTSD Scale for DSM-5 (CAPS-5). We excluded patients with severe visual or hearing impairment, neurological diseases, current addiction, pregnancy, intracranial metallic implants, psychotic disorders, or bipolar disorder. Randomization was stratified by center and depression severity, assessed using the Beck Depression Inventory (BDI) and categorized as BDI$\leq$16 or BDI$>$16. The tDCS group received active stimulation (20 minutes at 2mA) during script exposure (two sessions per day, interspersed by 20-min intervals, over five days). In comparison, the sham group received placebo stimulation (15 sec. ramp-up and down at session start and end) during the 10 script-exposure sessions. The script exposures, comprising factual, physical, and emotional elements, involved patients internally reading a self-written document accurately recalling the personal traumatic event [6]. The primary outcome was PTSD severity, assessed by the CAPS-5. The PTSD checklist scale (PCL-5) and BDI were secondary outcomes. All measures were apprehended at baseline, one (M1) and three months (M3) after the first treatment session. After one withdrawal of consent, 33 participants constituted the tDCS group and 29 participants the sham group (Supplementary figure 1 and table 3).

A sample size of 64 participants yielded 80 % statistical power to detect a 10-point difference between groups in the CAPS-5 score, assuming a standard deviation of 20 points, a correlation coefficient between repeated measures of a participant of 0.5 and a type I error set at 5 %. Changes in every outcome over the follow-up period were compared between groups using a linear regression mixed-effect model. Fixed effects were for the time, the treatment arm and the interaction term between time and treatment arm. We also included a subject random effect allowing for modelling the repeated measures in a same participant. Tests were two-sided and a p-value below 0.05 was considered significant. This study was approved (ANSM 2016-A01087-44; CPP 2016-R22) and registered (NCT02900053).

Sixty-two participants were included for analysis, from which 62 had contributed to measurements at baseline, 57 at M1, and 56 at M3. At baseline, the estimated mean CAPS-5 score was comparable between the sham group (42.2 $\pm$ 13.9) and the tDCS group (46.4 $\pm$ 11.6) (Fig. 1C and D). The CAPS-5 slope from baseline to M3 was -7.2 points per month (95 % CI -9.1 to -5.3) in the sham group and -4.7 points per month (95 % CI -6.5 to -2.9) in the tDCS group, with no significant difference between groups (the difference of slope between groups was 2.5 points per month, 95 % CI -0.2 to 5.1, $p = 0.064$). Concerning self-reported PTSD severity using the PCL-5, the outcomes aligned consistently with CAPS-5 scores. The PCL-5 slope over the 3 months was -6.8 points per month (95 % CI -8.9 to -4.8) in the sham group, and -4.2 points per month (95 % CI -6.1 to -2.4) in the tDCS group, without significant difference between groups (2.6 points per month, 95 % CI -0.2 to 5.3, $p = 0.068$). Additionally, for depressive comorbid symptoms, slope of the BDI score over the 3 months was -1.6 points per month (95 % CI -2.4 to -0.8) in the sham tDCS group and -1.7 points per month (95 % CI -2.5 to -0.9) in the tDCS group (the difference of slope between groups was -0.1 point per month, 95 % CI -1.2 to 1, $p = 0.837$). No between-group difference was found concerning other outcomes assessed such as anxiety, quality of life or cognitive performances (see supplementary file for more information). However, 10 tDCS sessions within five days were well tolerated and did not provoke any major adverse events.

No significant differences in the mean CAPS-5, PCL-5 or BDI scores were seen between groups. Consequently, our tDCS protocol targeting the left dlPFC might not be an appropriate protocol to combine with exposure therapy in PTSD patients when disease severity is evaluated at three months. Cathodal stimulation over the left dlPFC might have a greater influence in reducing PTSD symptoms and could be associated with anodal right dlPFC stimulation [7,8]. But the vmPFC could be further investigated as it was recently shown to reduce self-reported

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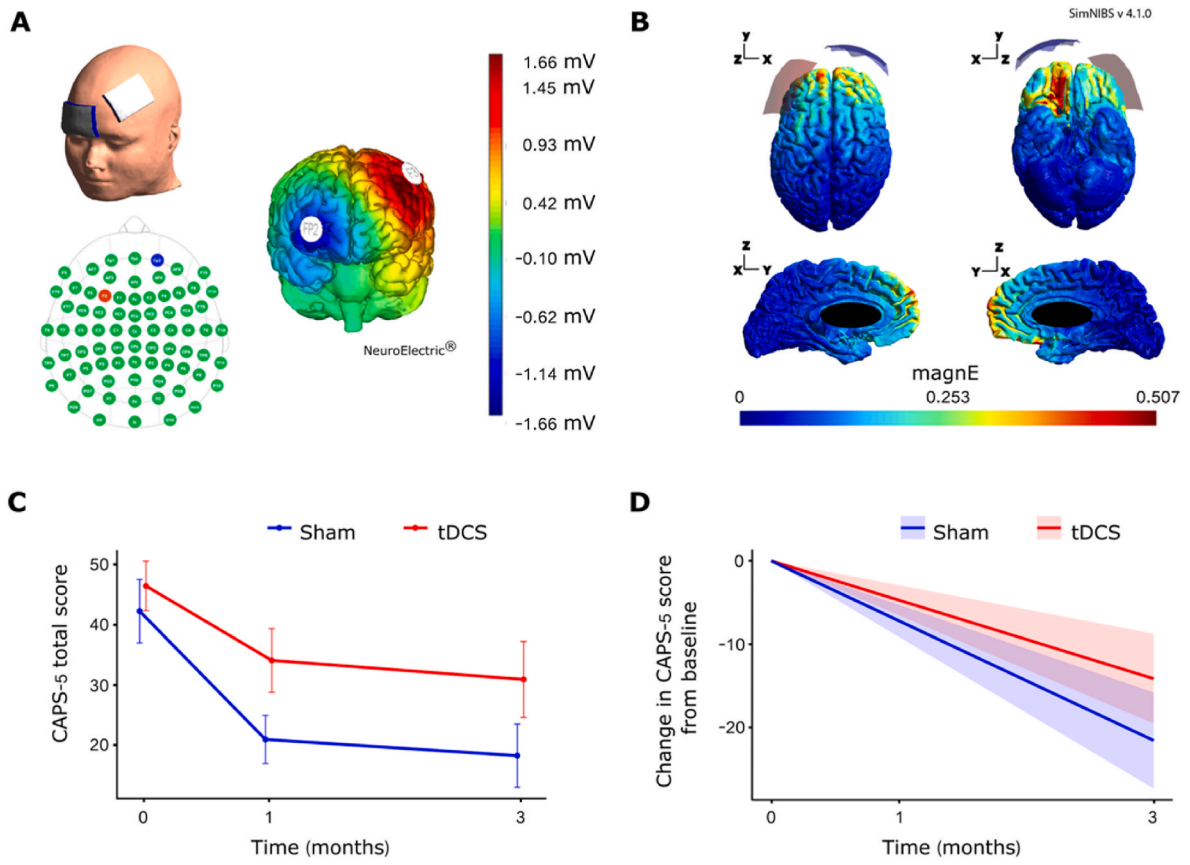

Fig. 1. (**A**) Experimental design of anode-cathode positioning (EEG 10–20 system) and current application representation. The anode (in red) was placed over the F3 coordinate and the cathode (in blue) over FP2. Electrodes measured 35 cm^2 each. (**B**) Electromagnetic field modeling (magnE) according to electrodes positioning with a 2-mA current application. (**C**) Plots of means by group of the CAPS-5 measured at baseline (time = 0), month 1 and month 3. Error bars are 95 % confidence intervals. (**D**) Slopes of change from baseline of the CPAS-5 score over the 3 months period of the trial according to the group of randomization:
slopes were estimated using a linear regression mixed effect model with time as a continuous variable and with an interaction term between time and group; colored shadows are the 95 % confidence interval of the slopes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

PTSD severity [9].

In conclusion, although well tolerated, active tDCS over the left dlPFC did not alleviate PTSD symptoms compared to sham stimulation. Anodal stimulation of the left dlPFC might not be efficacious in yielding beneficial effects when combined with script exposure. Further trials are needed, using different protocols and targeting other brain regions, to explore the efficacy of combining exposure procedures with tDCS.

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Data sharing statement

De-identified individual participant data will be made available to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. A written agreement must be signed with the University Hospital of Tours and the coordinator of the study.

CRediT authorship contribution statement

Noémie Eyraud: Writing – review & editing, Writing – original draft, Validation, Methodology. **Pierre Poupin:** Writing – review & editing, Visualization, Validation, Methodology, Data curation. **Marc Legrand:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Agnès Caille:** Writing – review & editing, Methodology, Data curation. **Anne Sauvaget:** Writing – review & editing, Methodology. **Samuel Bulteau:** Writing – review & editing, Methodology. **Bénédicte Gohier:** Writing – review & editing, Methodology. **Ghina Harika-Germaneau:** Writing – review & editing, Methodology. **Dominique Drapier:** Writing – review & editing, Methodology. **Nematollah Jaafari:** Writing – review & editing, Methodology. **Olivier Bodic:** Writing – review & editing, Methodology. **Bruno Brizard:** Writing – review & editing, Methodology. **Valérie Gissot:** Writing – review & editing, Methodology. **Catherine Belzung:** Writing – review & editing, Validation, Resources, Project administration, Conceptualization. **Jean-Baptiste Courtine:** Writing – review & editing, Validation, Conceptualization. **Wissam El-Hage:** Writing – review & editing, Project administration, Funding acquisition, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.04.018.

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