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Combining proactive transcranial stimulation and cardiac biofeedback to substantially manage harmful stress effects



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ABSTRACT

Background: Previous studies have identified the dorsolateral prefrontal cortex (dlPFC) as a core region in cognitive emotional regulation. Transcranial direct current stimulations of the dlPFC (tDCS) and heart-rate variability biofeedback (BFB) are known to regulate emotional processes. However, the effect of these interventions applied either alone or concomitantly during an anticipatory stress remains unexplored.

Objective: The study investigated the effect of anodal tDCS and BFB, alone or combined, on psychophysiological stress responses and cognitive functioning.

Methods: Following a stress anticipation induction, 80 participants were randomized into four groups and subjected to a 15-min intervention: neutral video viewing (CTRL), left dlPFC anodal tDCS (TDCS), heart-rate variability biofeedback (BFB), or a combined treatment (BFB + TDCS). Participants were then immediately confronted with the stressor, which was followed by an assessment of executive functions. Psychophysiological stress responses were assessed throughout the experiment (heart rate, heart-rate variability, salivary cortisol).

Results: The TDCS did not modulate stress responses. Compared with both CTRL and TDCS interventions, BFB reduced physiological stress and improved executive functions after the stressor. The main finding revealed that BFB + TDCS was the most effective intervention, yielding greater reduction in psychological and physiological stress responses than BFB.

Conclusions: Combining preventive tDCS with BFB is a relevant interventional approach to reduce psychophysiological stress responses, hence offering a new and non-invasive treatment of stress-related disorders. Biofeedback may be particularly useful for preparing for an important stressful event when performance is decisive.

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1. Introduction

Psychosocially stressful situations are common, and the current COVID-19 pandemic situation has considerably worsened the occurrence of stress-related disorders [1]. Stress arises when environmental demands exceed the adaptive capacity of the organism, resulting in biological, psychological, and behavioral changes [2]. The acute stress response, underpinned by the activation of the sympathetic and the withdrawal of the parasympathetic systems, causes an increase both of the activity of the sweat glands and of glucocorticoid secretions and a decrease in

heart-rate variability. When this stress response is recurrent, the risk of developing numerous physiological and psychological diseases, such as hypertension, burnout, generalized anxiety disorders, and depression, increases [2]. The stress response also affects major executive functions, such as working memory, flexibility, and inhibition [3–9]. Therefore, counteracting deleterious stress effects represents a crucial challenge in improving well-being and facing day-to-day constraints. Recent studies reported that cerebral stimulations and biofeedback might be relevant methods of counteracting particular facets of stress, but their potential preventive effects, notably the avoidance of cognitive deteriorations, remain to be determined [10–12].

Transcranial direct cerebral stimulation (tDCS) is a safe non-invasive technique, enabling the conditioning of the human cortex for up to 60 min, whereby anodal and cathodal stimulations respectively induce excitatory and inhibitory effects [13]. Anodal tDCS over the left dorsolateral prefrontal cortex (dlPFC) has been found to positively affect emotional regulation by reducing the perceived valence of negative stimuli, increasing heart-rate variability, and reducing cortisol levels [10,11]. Transcranial stimulation over the left dlPFC further contributed to improving many facets of performances [14] such as working memory [15–17], shifting [18], and inhibition abilities [19,20]. Nevertheless, only one study has tested the effect of anodal left dlPFC stimulation within a stressful context [21], showing a significant reduction in heart rate reactivity, but effects on cognition were not explored [21]. In light of these findings, further research investigating the preventive effects of left dlPFC stimulation on stress and cognitive deterioration is therefore warranted.

Another recent promising treatment for promoting emotion regulation is the heart-rate variability biofeedback (BFB) allowing to assess and display cardiac parameters in real time, hence fostering its conscious individual control. When paired with a slow-paced breathing exercise, BFB leads to an increase in heart-rate variability through respiratory sinus arrhythmia [12,22,23]. A shift in activation from the sympathetic to the parasympathetic branch of the central nervous system contributes to reducing psychophysiological stress markers [24,25]. In healthy adults, BFB contributes to improving vagal cardiac control and relaxation and reduces anxiety and subjective stress [26–30]. Early data indicated that a 10-min BFB intervention may improve cognition [28]. More recently, we found that 15 min of BFB improved the subjective performance of core executive functions [31]. Altogether, these results support the efficiency of BFB in stress coping, but its selective influence on executive skills during a stressful event remains to be determined.

The timing of the delivery of a coping intervention remains crucial to eliciting efficient stress management. It has been generally assumed that the stress response occurs in ego-threatening, uncontrollable, and unpredictable situations [32]. However, in many circumstances, stressful situations can be identified before the occurrence of the stressor [31]. The period of stress anticipation offers a great opportunity to practice preventive coping strategies, which should help to deal with the future stressor. Most of BFB and tDCS interventions have been implemented during or after the occurrence of the stressful event to foster stress recovery [12,21,30,33,34]. Recent data suggest that BFB intervention prior the stressful event contributed to decrease anticipatory stress [31]. Additionally, Carnevali (2019) reported a reduction in physiological stress markers and anxiety when applying tDCS over the left dlPFC just before and during a stressful event. However, they did not assess the effect of the stimulation during the anticipation of a stressful event. Therefore, it remains to be experimentally investigated how left dlPFC stimulation and BFB during the period of

stress anticipation might decrease the subsequent stress response and avoid cognitive deterioration.

The present study aimed to investigate whether heart-rate variability BFB and left dlPFC anodal tDCS during the anticipation of a stressful event might reduce the psychophysiological stress response and prevent further cognitive deterioration. According to the modulating effects elicited by BFB and tDCS *per se*, we tested for the first time their potentiated effects when applied concomitantly.

2. Methods and materials

2.1. Participants

Eighty-five healthy volunteers took part in the experiment. To be eligible, participants were required to be over 18 years of age, be right-handed (Edinburgh inventory score of >70), and have normal or corrected-to-normal vision. Exclusion criteria included self-reported history of head injury, regular drug use, contraindications for tDCS (e.g., head implant, pacemaker), diagnosed psychological disorders or chronic disease (e.g., epilepsy), and medication that could influence heart rate (e.g., beta-blockers, anti-anxiety medication). Participants received a detailed informative note and provided a written consent form in line with the Declaration of Helsinki [35]. The study was approved by the local institutional review board of the University.

2.2. Experimental design

Participants underwent two experimental sessions separated by at least one week (10 ± 3 days). In the first session, participants were tested in terms of three executive functions (Fig. 1A). In the second session, the impact of four experimental interventions (CTRL, BFB, tDCS, BFB + tDCS) delivered during the anticipation of a stressful event was determined. Immediately afterwards, participants were confronted with the stressor, which was followed by a second assessment of executive functions (Fig. 1B). To limit circadian effects, both sessions were scheduled during the afternoon (noon to 6 p.m.). Participants were asked to refrain from physical activity and food and caffeine intake 2 h before testing. Five participants were excluded from the analysis due to not obeying the instructions, leading to a final sample of 80 participants (22.71 ± 6.16 years old; 40 women; body mass index: 21.48 ± 2.18).

2.3. First experimental session

Participants were seated on a chair approximately 50 cm from a 17-inch computer screen. Anxiety trait (State-Trait-Anxiety Inventory; STAI-Y-B; Cronbach's α 0.90), level of vigilance (Stanford Sleepiness Scale; SSS), and level of subjective stress (Visual Analogue Scale 10 cm; VAS stress, from *zero* to *maximum*) were assessed [36,37].

2.3.1. Cognition

Participants undertook three randomized cognitive tasks assessing three main executive functions: shifting (Switch), working memory (3-Back), and inhibition (Stroop) (Fig. 2; Appendix Text A). Behavioral data were collected using the software PsyToolkit [38,39]. For all tasks, the maximal response time was 2 s, and feedback was provided. For the Switch task, the participants made a cued binary decision about one of two possible tasks (color or shape). For the 3-Back task, participants had to determine if a letter had earlier appeared three times among 15 possible letters that were presented separately in a randomized order. For the Stroop task, participants were asked to identify the colors of written words while ignoring the meaning of the word. We assessed the global

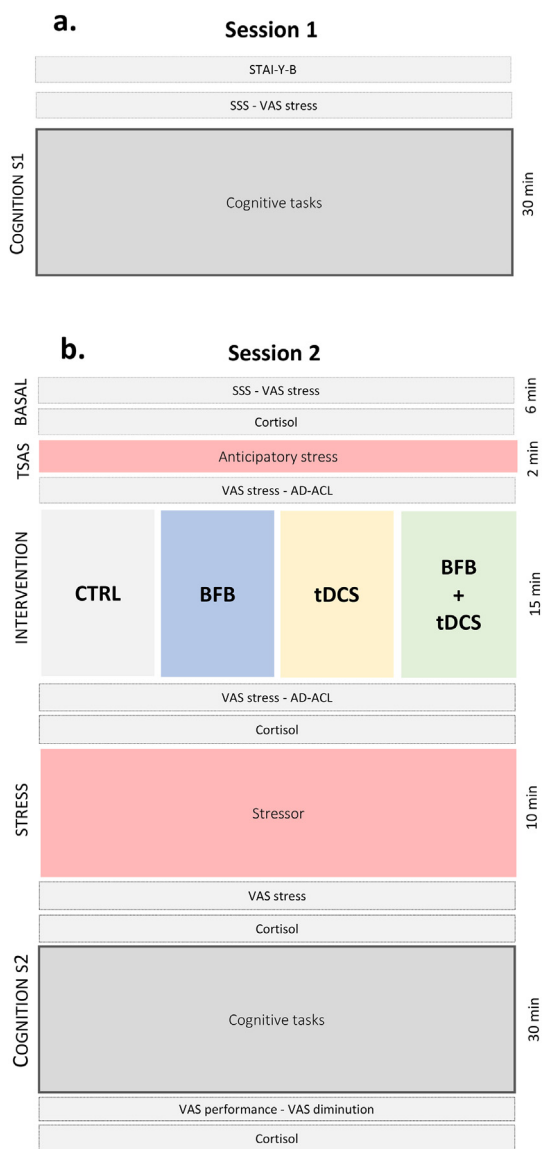


Fig. 1. Timeline of the experimental design. The cognitive tasks (Switch, 3-Back, Stroop) assessed the abilities of executive functions. The anticipatory stress was induced with Trier Social Anticipatory Stress (TSAS). Then, participants were randomly assigned to one of four intervention groups: neutral video (CTRL), heart-rate variability biofeedback (BFB), anodal dorsolateral prefrontal cortex stimulation (tDCS), or a combined method (BFB + tDCS). The acute stress was induced with the jury confrontation in the Trier Social Stress Test (TSST). Stress markers were assessed at different time-points (State-Trait-Anxiety Inventory; STAI-Y-B, Stanford Sleepiness Scale; SSS, Visual Analogue Scale; VAS stress, Activation–Deactivation Adjective Check List; AD-ACL, VAS performance, VAS diminution, cortisol) and continuously (cardiac parameters).

effect on executive performance by calculating two general performance scores based on error rates (ERs) and response times (RTs; in milliseconds) in each task:

- (1) error score: $(ER_{Switch} + ER_{3-Back} + ER_{Stroop})/3$
- (2) response time score: $(RT_{Switch} + RT_{3-Back} + RT_{Stroop})/3$

2.4. Second experimental session

Participants were first equipped with a connected tee-shirt allowing continuous tracking of cardiac activities (Hexoskin™; Carre Technologies Inc., Montreal, Canada). Then, the experiment was divided into five main periods: 6-min baseline (BASAL), anticipatory stress induction (Trier Social Anticipatory Stress; TSAS), intervention (INTERVENTION), stressor occurrence (STRESS), and cognitive tasks (COGNITION S2) (Fig. 1B). The same three executive functioning tasks were performed in the second experimental sessions.

2.4.1. Anticipatory stress

For the stress anticipation induction, participants performed the Trier Social Anticipatory Stress test (TSAS; 23). Participants were informed that, after 15 min of video viewing, breathing exercise, or cerebral stimulation, a panel of two people would evaluate their performance in two tasks (i.e., a job interview and mental arithmetic). The panel was always presented as hierarchical superiors of the experimenter. Participants were informed that performances would be video-recorded. Then, the experimenter left the room for 2 min.

2.4.2. Interventions

Once the experimenter returned to the experimental room, all participants were equipped with an ear pulse sensor recording their cardiac activity at 370 Hz (emWavePRO®; HeartMath Technologies; Add Heart®). Subsequently, they were allocated to a 15-min intervention following an *a priori* stratified randomization controlling for gender proportion: neutral video (CTRL, n = 20), heart-rate variability BFB (BFB, n = 20), dIPFC tDCS (tDCS, n = 20), or BFB paired with dIPFC tDCS (BFB + tDCS, n = 20).

2.4.2.1. Heart-rate variability biofeedback. For the BFB and BFB + tDCS interventions, the experimenter presented the visual interface composed of the cardiorespiratory signal and the breathing cursor displayed on a 17-inch computer screen (emWavePRO® interface). Participants were instructed to follow a standardized visual breathing cursor, leading inspiration and expiration at a rate of 6 breaths/min (Appendix Fig. B).

2.4.2.2. Transcranial direct cerebral stimulation. The tDCS (NIC2, NE®, v2.0.11.1, Barcelona, Spain) intervention was delivered in both the tDCS and BFB + tDCS groups through two saline-soaked sponge electrodes (25 cm²). An anode was localized over the left dIPFC and

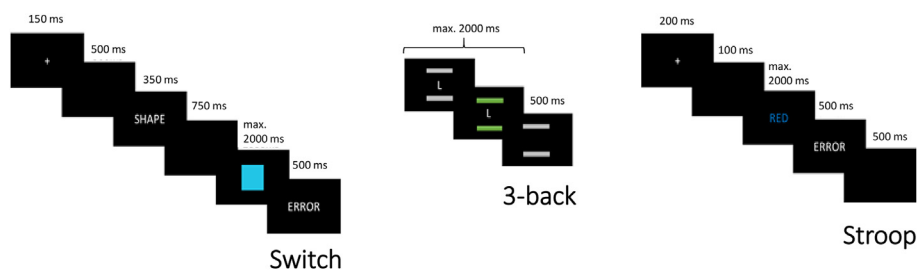


Fig. 2. Cognitive tasks. The Switch, 3-Back, and Stroop tests were performed to assess executive functions.

a cathode over the contralateral supraorbital area, referred to as F3 and Fp2, respectively (International 10–20 System). Electric stimulation was delivered for 15 min at 1.6 mA (current density = 0.064 mA/cm²), including 30 s of ramp-up/-down time (Fig. 3).

2.4.3. Stress

Immediately after the intervention, the experimenter left the room, while the panel of two people arrived. The panel always consisted of a woman and a man, who were unknown by the participant and blind to the type of prior intervention. The participants then underwent the Trier Social Stress Test (STRESS), which consisted of 5 min of a mock job interview followed by 5 min of a difficult mental arithmetic task in front of the panel composed of two cold experimenters [40,41].

2.5. Dependent variables controlling psychophysiological stress

2.5.1. Instantaneous psychometric measures

All participants rated how stressfully they experienced the immediate situation (VAS stress) at the beginning of session 2 (BASAL) and after the TSAS, the INTERVENTION, and the STRESS. Before and after the INTERVENTION, they completed the Activation–Deactivation Adjective Check List (AD-ACL) assessing the evolution of their relaxation and activation levels [42]. Internal consistency across the AD-ACL subscales at both measure points was acceptable (Cronbach's α 0.77 to 0.88).

2.5.2. Autonomic nervous system measures

The participants' average heart rates were recorded during the five experimental periods (BASAL, TSAS, INTERVENTION, STRESS, COGNITION s2). According to taskforce recommendations, heart-rate variability parameters were extracted from 5-min segments in the BASAL, INTERVENTION, STRESS, and COGNITION s2 periods. The detection of artifacts and extraction of time and frequency domains were performed using MATLAB software (R2019a®). For the time domain, we calculated the root mean square successive difference (RMSSD, in ms), the standard deviation of R–R intervals (SDRR, in ms), and the percentage of successive normal R–R intervals differing by more than 50 ms (pNN50, in ms). For the frequency domain, we quantified the power of low (LF: 0.04–0.15 Hz) and high (HF: 0.15–0.40 Hz) frequencies, then the ratio LF/HF was calculated. Saliva samples were collected before the BASAL and after the INTERVENTION, STRESS, and COGNITION s2 periods. Salivettes devices (Sarstedt®)

were conserved in ice before centrifugation (5 min, 5000 rpm) and stored at –20 °C. Salivary cortisol concentrations were assayed using a competitive enzyme-linked immunosorbent kit (Cortisol ELISA kit; abcam®).

2.5.3. Debriefing judgments

After the COGNITION s2 period, participants rated how the intervention enabled them to reduce their overall stress (VAS diminution, from *absolutely not* to *completely*) and influenced their performance in the cognitive tasks (VAS performance, from *negatively* to *positively*).

2.6. Statistical analysis

Statistical analyses were performed using the R freeware (v3.6.3). We used linear mixed effects with a by-subject random intercept (lme function, nlme package) [43]. All models tested the GROUP \times TIME interaction. To investigate the effect on VAS stress and heart rate, we entered TIME (BASAL, TSAS, INTERVENTION, STRESS, COGNITION s2) and GROUP (CTRL, BFB, TDCS, BFB + TDCS) as fixed effects. To examine the effect of GROUP on relaxation and activation levels, we entered TIME (PRE-INTERVENTION, POST-INTERVENTION) and GROUP. For heart-rate variability and cortisol analyses, we entered TIME (BASAL, INTERVENTION, STRESS, COGNITION s2) and GROUP as fixed effects. The effect on cognition (error score and response time score) was analyzed with TIME (SESSION 1, SESSION 2) and GROUP as fixed effects. The effects of GROUP on debriefing judgments (VAS diminution, VAS performance) were investigated with one-way ANOVAs. Visual inspection of the residual plots did not reveal any obvious deviation from homoscedasticity or normality. The statistical significance threshold was set for a type 1 error rate of $\alpha = 5\%$. Holm correction for multiple *post-hoc* testing was employed. Effects sizes were determined for GROUP (R_p^2 and η^2) and TIME (R_p^2) effects, as well as GROUP \times TIME (R_p^2) interaction, while Cohen's d were provided when comparing two groups. The intended sample size was calculated using G*Power (v3.1.9.4) for repeated measures and within-between interaction design. An *a priori* power calculation based on medium effect size ($f = 0.20$, $\alpha = 5\%$, $1 - \beta = 0.85$) resulted in a total sample size of 76 participants [44]. To prevent probable attrition, data losses or both, we recruited 10% additional volunteers ($n = 85$).

3. Results

All groups were equivalent in terms of demographic characteristics and exhibited similar anxiety traits and depressive symptoms. At the beginning of both sessions, all groups were also similar in subjective stress (VAS stress) and vigilance level (SSS) (Appendix Table C).

3.1. Analysis of dependent variables controlling psychophysiological stress

All significant GROUP \times TIME interactions are presented in Tables 1 and 2. All TIME and GROUP effects with *post-hoc* comparisons are detailed in Appendix Tables D and E, respectively.

3.1.1. Instantaneous psychometric measures

The analysis of VAS stress revealed no GROUP \times TIME interaction (χ^2 [12] = 18.69, $p = 0.10$), whereas the data for relaxation level showed a GROUP \times TIME interaction (χ^2 [3] = 16.14, $p = 0.001$, $R_p^2 = 0.03$); during the intervention, the relaxation level increased considerably more in the BFB + TDCS than in the CTRL group. A GROUP \times TIME interaction (χ^2 [3] = 12.89, $p < 0.01$, $R_p^2 = 0.04$) was

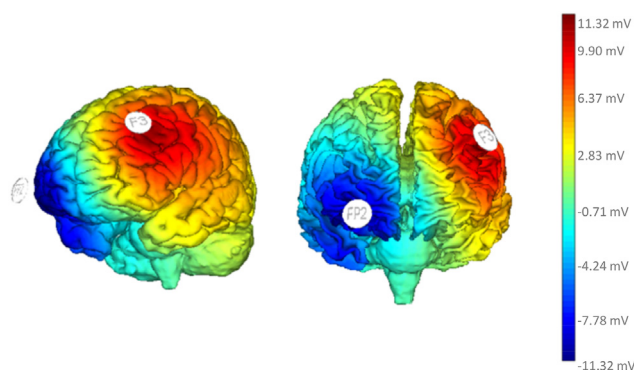


Fig. 3. Model of electric field induced by left dorsolateral prefrontal cortex anodal stimulation.

For transcranial direct cerebral stimulation (tDCS) interventions, an anode was situated over the left dorsolateral prefrontal cortex (F3) and a cathode placed over the contralateral supraorbital area (Fp2), according to the International 10–20 system. tDCS is a safe, non-invasive method.

Table 1
TIME × GROUP interactions for psychological stress markers.

TIME	GROUP	AD-ACL relaxation			AD-ACL activation		
		estimate	SE	p value	estimate	SE	p value
PRE-INTERVENTION VS	CTRL VS BFB	- 0.39	0.19	0.197	0.23	0.26	1.000
	CTRL VS TDCS	- 0.36	0.19	0.197	0.10	0.26	1.000
POST-INTERVENTION	CTRL VS BFB + TDCS	- 0.76	0.19	0.001	0.85	0.26	0.010
	BFB VS TDCS	0.03	0.19	0.891	- 0.12	0.26	1.000
	BFB VS BFB + TDCS	- 0.37	0.19	0.197	0.63	0.26	0.075
	TDCS VS BFB + TDCS	- 0.40	0.19	0.197	0.75	0.26	0.027

Values are expressed as estimated difference ± standard error (SE). Significant and trend (p < 0.10) post-hoc comparisons are in bold.

also found for the activation level, the decrease in activation being higher in the BFB + TDCS than in both CTRL and TDCS groups (Table 1).

3.1.2. Autonomic nervous system measures

3.1.2.1. Heart rate and heart-rate variability. Analysis of heart rate showed no GROUP × TIME interaction ($\chi^2 [12] = 13.09, p = 0.362$). Analysis of heart-rate variability showed a trend on RMSSD ($\chi^2 [9] = 16.55, p = 0.056$). Significant GROUP × TIME interactions were found for SDRR (Fig. 4A; $\chi^2 [9] = 36.49, p < 0.0001, R_p^2 = 0.05$) and pNNS50 values ($\chi^2 [9] = 21.30, p = 0.011, R_p^2 = 0.03$). The model of the LF/HF ratio also revealed an interaction (Fig. 4B; $\chi^2 [9] = 236.21, p < 0.0001, R_p^2 = 0.26$). Overall, post-hoc tests systematically demonstrated an advantage for interventions including BFB (i.e., BFB and TDCS + BFB) and additionally revealed a greater improvement in LF/HF ratio following TDCS + BFB intervention (Table 2). The improvement in LF/HF ratio is driven by an improvement of LF (Appendix Fig. F).

3.1.2.2. Cortisol.

No significant GROUP × TIME interaction was observed ($\chi^2 [9] = 10.86, p = 0.285$)

3.1.3. Debriefing judgments

The ANOVA on VAS diminution revealed a GROUP effect ($F_{3,76} = 6.39, p < 0.001, \eta^2 = 0.20$; Fig. 5A). Scores were higher in the

Table 2
TIME × GROUP interactions for physiological stress markers.

TIME	GROUP	SDRR			pNNS50			LF/HF		
		estimate	SE	p value	estimate	SE	p value	estimate	SE	p value
BASAL VS	CTRL VS BFB	- 29.77	8.04	0.010	- 5.75	3.85	1.000	- 0.786	0.106	< 0.001
	CTRL VS TDCS	- 3.53	8.24	1.000	- 0.23	3.95	1.000	0.023	0.108	1.000
INTERVENTION	CTRL VS BFB + TDCS	- 32.81	8.24	0.003	- 10.11	3.95	0.390	- 1.095	0.108	< 0.001
	BFB VS TDCS	26.23	7.92	0.031	5.53	3.79	1.000	0.809	0.104	< 0.001
	BFB VS BFB + TDCS	- 3.04	7.92	1.000	- 4.35	3.79	1.000	- 0.309	0.104	0.073
	TDCS VS BFB + TDCS	- 29.28	8.12	0.013	- 9.88	3.89	0.402	- 1.119	0.107	< 0.001
INTERVENTION VS	CTRL VS BFB	- 25.47	8.24	0.043	- 5.68	3.85	1.000	- 0.728	0.106	< 0.001
	CTRL VS TDCS	1.20	8.24	1.000	- 5.05	3.95	1.000	0.040	0.108	1.000
STRESS	CTRL VS BFB + TDCS	- 28.37	8.24	0.022	- 14.58	3.95	0.010	- 1.070	0.108	< 0.001
	BFB VS TDCS	26.68	7.92	0.027	0.63	3.79	1.000	0.768	0.104	< 0.001
	BFB VS BFB + TDCS	- 2.89	7.92	1.000	- 8.90	3.79	0.615	- 0.342	0.104	0.027
	TDCS VS BFB + TDCS	- 29.57	8.12	0.012	- 9.53	3.89	0.500	- 1.110	0.107	< 0.001
STRESS VS	CTRL VS BFB	- 1.11	8.04	1.000	1.98	3.85	1.000	0.062	0.106	1.000
	CTRL VS TDCS	- 1.08	8.24	1.000	8.54	3.95	0.917	- 0.028	0.108	1.000
COGNITION S2	CTRL VS BFB + TDCS	2.15	8.24	1.000	8.78	3.95	0.817	0.016	0.108	1.000
	BFB VS TDCS	0.03	7.92	1.000	6.56	3.79	1.000	- 0.090	0.104	1.000
	BFB VS BFB + TDCS	3.26	7.92	1.000	6.79	3.79	1.000	- 0.046	0.104	1.000
	TDCS VS BFB + TDCS	3.23	8.12	1.000	0.24	3.89	1.000	0.043	0.107	1.000

Values are expressed as estimated difference ± standard error (SE). Significant and trend (p < 0.10) post-hoc comparisons are in bold.

BFB + TDCS than in the CTRL (Cohen's d = 1.29), BFB (Cohen's d = 0.81), and TDCS groups (Cohen's d = 1.24), highlighting that combined intervention was judged as the most efficient intervention for reducing stress. The ANOVA on VAS performance revealed a main GROUP effect ($F_{3,76} = 7.47, p < 0.001, \eta^2 = 0.23$). Participants in both BFB groups estimated that the intervention had a positive impact on their cognitive performance, and this impact was better compared to the CTRL (CTRL VS BFB Cohen's d = 0.94, CTRL VS BFB + TDCS Cohen's d = 1.27) and TDCS groups (TDCS VS BFB Cohen's d = 0.82, TDCS VS BFB + TDCS Cohen's d = 1.13) (Fig. 5B).

3.2. Analysis of executive cognitive functions

Analysis of error rates revealed a GROUP × TIME interaction ($\chi^2 [3] = 14.58, p = 0.002, R_p^2 = 0.03$), showing that improvement in accuracy was greater in the BFB group (Table 3). In addition, improvement was slightly higher in the BFB + TDCS than in the TDCS group (no significant). Analysis of response times showed no GROUP × TIME interaction ($\chi^2 [3] = 5.04, p = 0.168$). Raw data with GROUP and TIME effects are presented in Appendix (Table G).

4. Discussion

This study investigated whether interventions of dlPFC anodal tDCS and BFB delivered – alone or concomitantly – during an anticipatory stress period might contribute to decreasing the psychophysiological stress response and further preserve executive abilities. The findings revealed a selective effect of these treatments

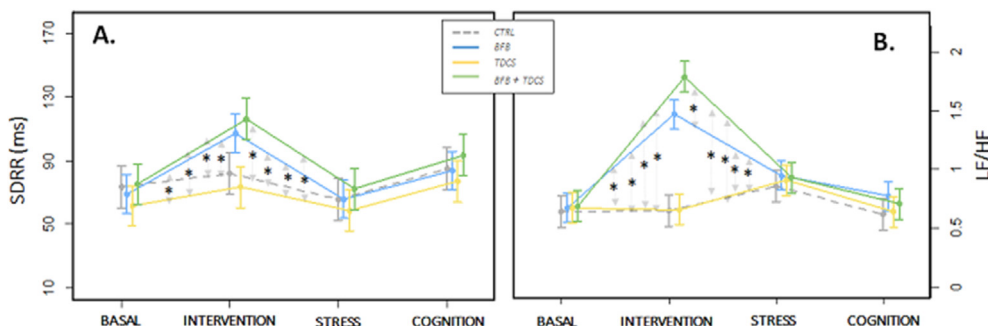


Fig. 4. Evolution of heart-rate variability.
The figure displays GROUP × TIME interactions with 95% confidence intervals. (A) SDRR. (B) LF/HF ratio.

on the psychological, physiological, and cognitive responses of stress. Proactive short BFB treatment reduced physiological stress and improved accuracy performances in executive functions, while combining BFB with tDCS strongly alleviated physiological and psychological stress responses. No effects of tDCS over the dlPFC were detected, when applied alone.

The first main finding of the present study is that physiological responses of stress were substantially reduced after 15 min of BFB applied alone during the anticipation of a stressful event. Participants subjected to the BFB experienced improved heart-rate variability features (SDRR, pNN50, LF/HF). Heart-rate variability is a reliable indicator of the adaptability of an organism and can be considered a relevant marker of health [12,23,25,45,46]. Our results reinforce previous findings suggesting that BFB is an efficient coping method for reducing psychophysiological stress responses [26–29,47]. More importantly, present data showed that proactive BFB has long-lasting effects on cognitive responses; following the stressful event, participants from the BFB group had the greatest improvement in the accuracy of executive functioning. The cognitive benefits induced by BFB intervention were reinforced by the subjective ratings. Both BFB groups, alone or combined with tDCS, judged that their intervention had a positive influence on their cognitive abilities. Although exploration of BFB effects on cognitive performance remains sparse [28,31], the positive impact of BFB on sport performance has been investigated more extensively [48]. Together, our results extend previous findings supporting the benefits of BFB on performance. Furthermore our findings

demonstrated, for the first time, the preventive effects of BFB applied during an anticipatory stress on following cognitive performance.

A second important finding is that combining BFB and tDCS contributed substantially to managing stress. The concomitant effect of the BFB + TDCS intervention induced a significant improvement in heart-rate variability along with a strongly potentiated LF/HF ratio. The LF/HF ratio provides information about the relationship of vagal input to the other causes of variability [23,49,50]. During periods of slow respiration rates, vagal activity generates oscillations in the LF band [50]. Thus here high LF/HF ratio is ought to reflect a greater vagal cardiac control. A recent review article highlighted the importance of stimulating the vagus nerve for improving resilience, notably for coping with the COVID-19 [1]. The improvement is thought to rely on body–mind interactions, which are carried out via a bidirectional communication pathway between the central nervous system and the body through the vagus nerve [1]. Here, the increased LH/HF ratio through the BFB + TDCS intervention might offer an efficient non-invasive method of simulating the vagus nerve. The subjective assessments also confirmed the positive effects of combining BFB and tDCS, which led to a greater level of relaxation during the anticipation period, similarly the debriefing judgments attested the highest decrease in the perceived stress throughout the experiment.

These original results demonstrate that the combined BFB + TDCS intervention is a relevant, safe, and effective proactive coping method. In addition, our results provided empirical data for the

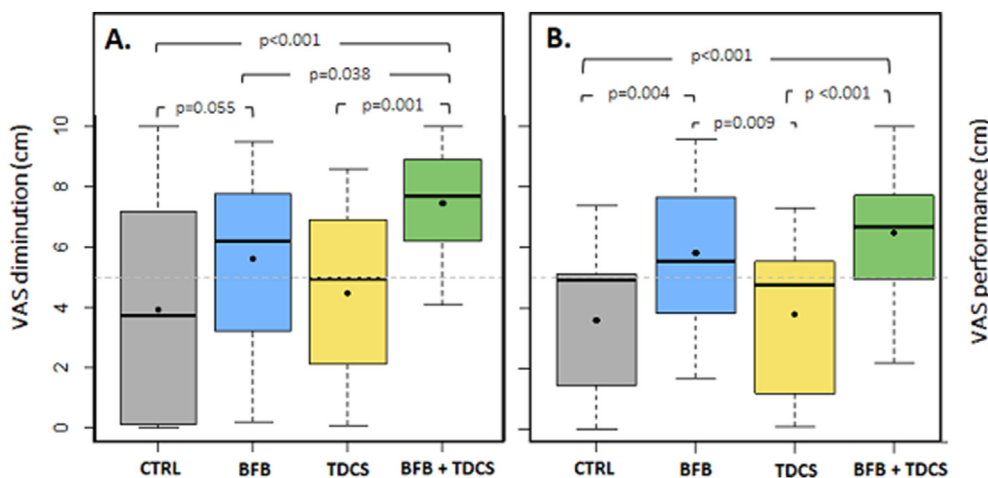


Fig. 5. Debriefing judgments.
(A) Subjective impact of the intervention on global stress diminution (from 0 = *absolutely not*, to 10 = *completely*). (B) Subjective impact of the intervention on performance (from 0 = *negative*, to 10 = *positive*). A score equal to five represented a null effect.

Table 3
TIME × GROUP interactions for error score.

TIME	GROUP	Error score		
		estimate	SE	p value
SESSION 1 VS	CTRL VS BFB	1.48	0.55	0.044
SESSION 2	CTRL VS TDCS	- 0.40	0.56	0.799
	CTRL VS BFB + TDCS	1.00	0.57	0.240
	BFB VS TDCS	- 1.88	0.56	0.007
	BFB VS BFB + TDCS	- 0.48	0.57	0.799
	TDCS VS BFB + TDCS	1.40	0.57	0.066

Values are expressed as estimated difference ± standard error (SE). Significant and trend ($p < 0.10$) post-hoc comparisons are in bold.

recent hypothesis of Mather and Thayer (2018), who suggested that high-amplitude oscillations in heart rate induce oscillatory activity in the brain, which enhances connectivity in the brain networks associated with emotion regulation (e.g., amygdala, medial prefrontal regions) [51]. Multi-sessions of BFB and anodal tDCS over the left dlPFC were found to substantially decrease stress-related symptoms in individuals suffering from generalized anxiety disorders, post-traumatic stress syndrome, and depression [45,52–57]. The present results are therefore of major importance for the design of innovative combined BFB and tDCS interventions and should now be confirmed in patients suffering from stress-related disorders before being implemented in clinical settings. While fixed 6 bpm breathing is convenient and efficient [23,29,31,58], future studies investigating long term effects of combined BFB and tDCS might benefit from *a priori* determination of individual resonance frequency following Lehrer's procedure [22]. Training individual to their own respiratory frequency is expected to be more comfortable for participant and further potentiate the biofeedback effectiveness of repeated interventions. Finally, the impact of BFB + TDCS on executive functions revealed mixed effects. Although debriefing judgments suggested that participants in the BFB + TDCS group felt that they were more efficient during cognitive assessments, behavioral data were not congruent. As the BFB + TDCS participants demonstrated the lowest score in activation level following the intervention, we postulate that a deactivation might have affected the optimal arousal level needed to perform well in the cognitive tasks [59]. This remains a working hypothesis awaiting further experimental investigation.

Surprisingly, our data did not reveal significant improvement in psychophysiological stress markers and cognition following the tDCS intervention. To date, there is no clear consensus regarding the effects of dlPFC stimulation on emotional regulation. Some authors reported no impact at all [60,61], whereas others observed greater emotional regulation [11,21,62]. One possible explanation for this discrepancy may relate to the difference in the timing of the stimulation, where benefits to emotional regulation might be restricted to concomitant stimulation and stress event occurrence [21]. Similarly, positive effects on cognition were most frequently reported when the cerebral stimulation was applied during the cognitive tasks [63,64]. The lack of further improvement in cognition in the tDCS group might also be explained by the site of the stimulation [65]. Other sites of stimulation, such as the inferior frontal gyrus, the inferior frontal cortex, or the left parietal cortex, might be more relevantly targeted to increase cognitive performance [66–69]. One another possible explanation for the absence of tDCS effects is the relatively low spatial resolution of tDCS, which enable cortical areas adjacent to the dlPFC to also receive stimulation. Nevertheless, the brain current density is expected to be highest in cortical areas that are directly below the anodal electrode and decreases as the distance from the electrodes increases [70,71]. Overall, interpreting the lack of effects of tDCS in the present study

remains difficult due to the absence of previous experimental work dealing with the interaction between stress, cerebral stimulation, and cognition. Futures investigations should specifically examine the optimal tDCS parameters that might contribute to emotional regulation in the context of stress.

This study had some limitations. As executive function skills are highly dependent on the individual, this study opted for an intra-individual design to limit group effects. One unexpected finding was the improvement of both response time and accuracy in all groups, supporting a learning effect without additional enhancement after cerebral stimulation. It is possible that a learning effect somewhat masked putative additional benefit. An important point to raise is the self-reported nature of disease, smoking habit, and/or drug use by the participants when engaging in the experiment. As no physical or laboratory examination was performed, one cannot completely exclude the possibility of hidden chronic disease or drug use in this population, which may have influenced the effects of the intervention. Further studies controlling for learning effects are also necessary to understand in greater detail how BFB and tDCS may interact with cognition in a stress context. Finally, our design did not include sham groups, and future studies might include sham-condition and/or a reversed polarity brain stimulation setting. In particular, the effects of preventive sham-tDCS paired with biofeedback should be considered for a better understanding of the additional effects of tDCS.

5. Conclusions

To conclude, stress is an important societal problem inducing numerous consequences in wellbeing and health, and the development of effective methods that can be applied before the occurrence of a stressful event are necessary to prevent the earliest possible manifestation of stress. The present findings demonstrated the additive contribution of short proactive BFB with left dlPFC stimulation in reducing the psychophysiological stress response. While applying tDCS before a day-to-day stressful event might not be easily achievable, its application in the clinical setting seems appropriate [65]. Multi-sessions of BFB practice and left dlPFC stimulation have been independently established as relevant techniques in a clinical population suffering from stress disorders. Accordingly, our results provide a rationale for further exploration of whether BFB paired with left dlPFC stimulation might alleviate stress-related disorders. In addition, we found, for the first time, that delivering a short BFB intervention during the stress-anticipation period was likely to improve executive performance. As BFB offers rapid effects without being resource intensive, present results encourage the practice of BFB in real-life stress-anticipation events where a high level of performance is expected, such as before a job interview or sport competition.

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None.

Declarations of interest

None.

CRedit authorship contribution statement

Sophie Schlatter: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Aymeric Guillot:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Laura Schmidt:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Mathilde Mura:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Robin Trama:** Formal analysis, Investigation, Visualization, Writing – review & editing. **Franck Di Rienzo:** Formal analysis, Investigation, Supervision, Writing – review & editing. **Marc Lilot:** Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Ursula Debarnot:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing, Writing – original draft, Validation.

Declaration of competing interest

We have no competing interests.

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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.2021.08.019>.

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