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Transcranial direct current stimulation associated with physical exercise can help smokers to quit smoking: a randomized controlled trial

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Chronic exposure to nicotine is related to low activity in the prefrontal cortex and insular hyperactivity in smokers. Therefore, addiction has been the target of experimental studies in aerobic exercise (AE) and transcranial direct current stimulation (tDCS). Thus, the objective of this study was to verify the effect of AE and anodal tDCS at F4 and cathodal at T3 on craving, motivation to change smoking behaviour (MCSB) and brain reactivity (BR) in smokers. The sample consisted of 41 chronic smokers distributed into four groups: tDCS (G1), AE (G2), tDCS combined with AE (G3) and sham tDCS combined with AE (G4). All volunteers underwent 5 consecutive sessions of the intended intervention. Before starting the intervention protocol and after the last intervention session, the volunteers answered questionnaires and underwent an electroencephalogram exam, to evaluate the variables investigated. The results demonstrated that AE, when associated with active tDCS, was effective in promoting a reduction in craving ($p < 0,05$), cigarette consumption ($p < 0,05$), and BR ($p < 0,05$) during exposure to smoking cues, in addition to increasing MCSB ($p < 0,05$). Therefore, only when associated with AE, tDCS was able to modulate positive effects on smoking.

Recent data from the World Health Organization (WHO) show that smoking is the main cause of preventable death in the world[1]. The addictive effects of smoking arise mainly from the actions of nicotine on the central nervous system (CNS), with this psychoactive constituent of tobacco being a stimulant of the dopaminergic system of the mesolimbic pathway, which originates in the ventral tegmental area to the nucleus accumbens and projects into areas related brain cells, such as the prefrontal cortex (PFC)[2]. Prolonged exposure to nicotine contributes to a reduced activity of reward-related circuits during abstinence, especially the PFC, and correlates with high levels of impulsivity and craving[3]. Therefore, treatments targeting PFC activation offer a new therapeutic approach to smoking cessation.

In this sense, several studies[4–6] point to transcranial direct current stimulation (tDCS) as a likely effective technique in reducing craving and consumption of cigarettes, in addicted subjects, encouraged by the observation of increased dopamine (DA) release (via anodal stimulation) and the close connection between the dopaminergic system and improvement in cognitive aspects and attention[7,8]. tDCS is a non-invasive brain stimulation procedure that delivers a direct current through electrodes placed on the scalp, capable of altering the membrane potential of neurons and inducing action potentials in cells, modulating neural activity in superficial and underlying regions[9]. Traditionally, anodal stimulation increases neuronal excitability of cells, while cathodal stimulation decreases it[10]. However, it has been observed that the relationship between stimulation and neural response depends not only on the type of electrode, but also on the length and strength of the stimulation applied through it[9], so that anodal tDCS can lead to decreased excitability when the stimulation time is increased[11], and cathodal tDCS can lead to increased excitability when the intensity is increased[12]. These phenomena can induce neuroplasticity[10].

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Neuroplasticity involves long-term potentiation and long-term depression, which depend on postsynaptic calcium levels, with the involvement of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, metabotropic glutamate receptors, as well as gamma-aminobutyric acid (GABA)-A and GABA-B receptors[10]. Talar et al.[13], argue that one option to increase neuroplasticity induced by tDCS is its pairing with aerobic physical exercise, as both share common neural substrates. Therefore, it is conceivable that synergistic effects on the PFC can be produced and lead to a higher efficacy rate than that achieved with each intervention alone.

In fact, physical exercise (PE) has been identified as a non-pharmacological intervention in the treatment of chemical dependency (CD)[14,15]. Image studies demonstrate an increase in PFC activity during aerobic exercise (AE) at submaximal intensities and a decrease in craving in subjects involved in EFA programs[16]. Steinberg et al.[17] also verified through a literature review the effects of tDCS and AE on cognitive functions and their possible synergies, concluding that the combination of tDCS and AE offers multiple beneficial opportunities in the treatment of various psychiatric and neurological conditions.

The tDCS protocol used in this study, anode in the PFC in F4 and the cathode in the temporal region in T3, is based on several arguments related to the functions of these brain regions and their impact on nicotine dependence. For example: the F4 region is strongly related to executive control and inhibitory regulation, which are crucial for impulse control and decision-making related to substance use, such as cigarettes. For this reason, this has been a target region of anodal tDCS in smokers[4,5]. The T3 region plays a role in emotional perception and in the regulation of behaviors in stressful situations, mediated by the amygdala and insula, since their hyperactivity influences the consumption of substances, such as cigarettes[18]. On this subject, Montenegro et al.[19] when stimulating the temporal region in T3 observed responses in the insular region, while Ibrahim et al.[20] advocate the use of brain stimulation in the insular region, as it is a critical area involved in smoking addiction.

In this sense, another important variable to be investigated is brain reactivity (BR) to cigarette smoking cues. BR is a wide range of responses displayed when subjects are exposed to contextual and conditioned stimuli associated with substance use[21]. For example, gamma activity is increased in smokers when compared to non-smokers[22], in several specific regions, including the PFC, especially when exposed to conditions that increase the degree of desire. This occurs through the action of receptors such as glutamate, the main excitatory neurotransmitter of the CNS[23]. Thus, high gamma activity is strongly associated with the risk of relapse in drug seeking[24]. Recent meta-analyses[25,26] indicate that participants who showed greater BR to smoking suggestions had greater cravings and the likelihood of relapse[21].

Thus, the objective of the present study was to verify the effect of tDCS associated with AE on craving, motivation to change smoking behaviour (MCSB) and which brain regions are activated during exposure to cigarettes. It was hypothesized that during cigarette exposure there would be a significant decrease in gamma waves and craving, as well as an increase in MCSB in the tDCS + AE group.

Methods

Participants

To estimate the sample size, the statistical software G-Power version 3.1.9.4 was used. It was calculated that a sample of 48 participants would be required to detect a medium effect ($f = 0.25$) with 80% power and $\alpha = 0.01$. The effective size of $f = 0.25$ was calculated based on the study by Mondino et al.[6]. We estimated a 10% attrition rate and thus planned to recruit 52 participants. Participants were recruited through social networks and bulletin boards in health centers in the city of Maceió/Alagoas. The health centers selected for posting the flyers were those that had patients on the waiting list to join the smoking cessation program. This program was offered in five centers throughout the city. However, one of them was temporarily closed, and the other, as it was linked to a psychosocial care institution specialized in alcohol and other drugs, had a target audience that might not fit the study. Therefore, three centers were included in the study. Both on social media and on the flyers, the researchers' phone and email contact information were available. After the volunteers reached out, the researchers scheduled an initial visit to verify whether the volunteers met the inclusion criteria. The inclusion criteria were being addicted to nicotine for more than 2 years, aged between 25 and 55 years. Volunteers were excluded from the study if they had substance abuse or addiction other than nicotine dependence, were diagnosed with a mental disorder, epilepsy, seizures, delirium tremens, chronic obstructive pulmonary disease, used psychotropic medication, were undergoing treatment for smoking cessation, any contraindication for electrical brain stimulation procedures such as electronic implants or metallic implants in the head, gestational status, presented physical and/or physiological problems that would interfere with participation in a moderate intensity physical exercise (PE) program, presented a moderate or high risk for the practice of PE. Finally, they would need to be available to participate for 5 consecutive days at fixed times in the interventions proposed by the research. The different groups were randomized using the block method (block size: 4) and the participants were not aware of the intervention condition. The volunteers were distributed into four distinct groups: tDCS (G1; $n = 13$); AE (G2; $n = 13$); tDCS + AE (G3; $n = 13$) and sham tDCS + AE (G4; $n = 13$). Of the 52 participants, 11 dropped out of the study. Reasons for dropping out were: schedule issues ($n = 5$; 2 in G1 and 3 in G4), and little motivation to complete the sequence of visits ($n = 6$, 1 in G1, 4 in G2 and 1 in G3). Thus, 41 participants were considered for analysis. Of these, 39% were women and 61% were men, distributed as follows: tDCS (G1, $n = 10$); AE (G2, $n = 9$); tDCS + AE (G3, $n = 12$) and sham tDCS + AE (G4, $n = 10$). The study was approved by the Research Ethics Committee of the Federal University of Alagoas (n° 2.896.666), by the declaration of Helsinki (1964) and was registered in the Brazilian Registry of Clinical Trials (ReBEC) (n° RBR-4dh99pj) in 26/06/2024 https://ensaiosclinicos.gov.br/rg/RBR-4dh99pj, Universal Trial Number (UTN) (U1111-1307-1006). The date that the first volunteer showed up to start the sessions was 14/03/2019. All participants gave their informed consent before participating in the study.

Experimental design

Volunteers able to participate in the research were familiarized with all study equipment and procedures and invited to attend 5 consecutive visits to the laboratory, from Monday to Friday (V1-V5). On the first visit (V1) they answered questionnaires regarding the level of nicotine dependence (Fagerström), the level of craving (QSU-B) and the level of MCSB (URICA). V1 was carried out on a Monday and in addition to the questionnaires, carbon monoxide (CO) levels were checked, the number of cigarettes smoked in the last three days, and the EEG exam was carried out, immediately followed by the first session of the intervention to which the volunteer was assigned. In the following visits, V2 to V5 (Tuesday to Friday), the interventions continued, with the volunteers reporting the number of cigarettes smoked since the last intervention to date. At the end of the last intervention session (V5), the volunteers were again subjected to the evaluation procedures carried out in V1: Fagerström, QSU-B, URICA, CO levels and EEG examination. During the EEG examination, participants were exposed to cigarette smoke signals to check brain reactivity. Craving was assessed before and after each cigarette exposure. The entire test and intervention protocol was standardized. The application of questionnaires, EEG examination and CO measurement was carried out by only two evaluators, and to guarantee greater psychometric quality of the data, the volunteer who was evaluated in V1 by the evaluator was reassessed at V5 by the same evaluator.

Fagerström test

The Fagerström Test for Nicotine Dependence aims to estimate the degree of nicotine dependence, demonstrating good psychometric qualities in terms of validity, reliability, and reproducibility[27]. The questionnaire contains 6 questions and the calculation of the points obtained in each question determines how dependent a patient is on nicotine. Score: 0–2 points: very low dependence; 3–4 points: low dependence; 5 points: medium dependence; 6–7 points: high addiction; 8–10 points: very high addiction.

Craving induction and assessment

Studies have shown[28,29] that exposing individuals to drug-related environmental stimuli reliably triggers craving for the drug. Ferguson et al.[30] report that studies of exposure to stimuli related to cigarette addiction have a relatively standard procedure, in which subjects are instructed to hold and manipulate a cigarette, and/or through exposure to images (e.g., a video of people smoking). Following these guidelines, participants were engaged in multiple sensory modalities (visual, olfactory, and tactile) and, therefore, closer to a realistic exposure. Participants were instructed to bring their preferred cigarette on the days of the EEG scan and to induce craving, they watched a one-minute video showing scenes of people smoking in four trigger contexts: loneliness, partying, stress, and coffee. They were then instructed to pick up the cigarette and hold it between their fingers while at the same time being exposed to its odor, positioned close to their nostrils. These procedures were standardized to be performed for 60 s each.

Immediately after the end of the EEG exam, the craving was assessed using the Questionnaire of Smoking Urges-Brief (QSU-B)[31]. This questionnaire consists of ten affirmative questions, to which the individual positions themselves using a seven-point scale ranging from "completely disagree" to "completely agree". The QSUB can be analyzed through the total sum of points. If you get 0 to 13 points, the classification is minimal craving; from 14 to 26, light; from 27 to 42, moderate; and 43 or more points, intense craving. This questionnaire was applied in V1 and V5.

Assessment of motivation to change smoking behaviour (MCSB)

To assess the MCSB, the Rhode Island Change Assessment Questionnaire[32] was used, which investigates the motivational stages of patients seeking treatment to modify any type of behavioral problem. It contains 32 questions divided into four subscales, which cover the following stages of behavioral change: pre-contemplation, contemplation, action, and maintenance and aims to provide this information to help guide appropriate treatment approaches. This questionnaire is considered a reliable instrument with good internal consistency in patients with CD, especially from cigarette smoking.

Carbon monoxide (CO) measurement

To verify smoking status and measure cigarette consumption, volunteers were instructed to remain smoke-free for at least 30 min before providing CO level readings at V1 and immediately after V5. To this end, a piCO + TM Smokerlyzer® carbon monoxide monitor (Bedfont Scientific Ltd., Kent, England) was used. This device measures the concentration of CO in exhaled air in particles per million (ppm). In this way, CO concentrations were measured through slow and continuous exhalation through the mouthpiece of the device, after a forced apnea of 15 s. The reading immediately appears on the display during the test. The volunteers repeated this protocol 3 times and the final mean CO concentrations were used for data analysis.

Cigarette consumption

Cigarette consumption was assessed using a diary in which volunteers indicated the number of cigarettes smoked per day. They kept a record of consumption in the last three days before starting the research and daily during the intervention period. As explained above, this variable was also measured by measuring CO levels.

Assessment of brain electrical activity

Brain electrical activity was recorded using the EMSA64 Nano quantitative electroencephalogram (EEG), from the company EMSA, with 20 channels, a sampling frequency of 256 points gamma frequency.

For the analysis of the EEG signal, a spectral analysis was used using a Fourier transformation. Eras with gimmicks were excluded from the analysis. Power band values were calculated by summing the power across all bins at alpha (8–13 Hz) and gamma (30 to 45 Hz) frequency. Scalp electrode placement was performed

according to the international 10–20 system, with 23 electrodes (FPZ, FP1/FP2, F7/F8, T3/T4, T5/T6, F3/F4, C3/C4, P3/ P4, O1/O2, FZ, CZ, PZ and OZ, A1/A2), an arrangement that is in line with that recommended by the American EEG Society[33]. EEG analysis was performed by quadrant, with the left anterior region (LA) corresponding to F3, F7, T3 and C3, the right anterior region (RA) to F4, F8, T4 and C4, the left posterior region (LP) to T5, P3 and O1 and the right posterior region (RP) corresponding to T6, P4 and O2.

Volunteers were instructed to have clean and dry hair on the day of the exam. The EEG was performed in 2 standardized time windows, most of it between 9 am and 12 pm, and a small part from 2 pm to 4 pm. Participants were instructed to remain seated, avoid movement and not speak during the examination. They were then instructed to follow some commands: first, close their eyes for 2 min (closed eyes - CE), then open their eyes and watch a video with the content of people smoking for 1 min (video - task 1 (T1)), and, finally, handle a cigarette of their choice for 1 min (manipulation - task 2 (T2)) at the same time they were exposed to the smell of cigarettes.

This exposure to cigarette signs sought to induce craving and thus verify CR through the electroencephalographic recording of alpha and gamma waves, which respectively measure the deactivation and activation of the cortical area.

Active tDCS protocol

Volunteers were recommended to have clean and dry hair on the days of the sessions, free of creams and/or gels and not to use metallic objects on their heads, such as hairpins, piercings, or other types of metallic accessories during the sessions. To perform the session, volunteers sat in an armchair while the standard procedure was carried out. First, the electrodes were fixed using elastic bands. The arrangement of the electrodes followed the international 10–20 electroencephalogram system, as recommended by the American EEG Society[33]. The anode was positioned on the right side in the prefrontal region (F4) and the cathode was positioned on the left side in the temporal region (T3). The two electrodes of different sizes, the 5×5 anode (25 cm^2) and the 5×7 cathode (35 cm^2) were covered with sponges soaked in saline solution (140 mmol of NaCl dissolved in Milli-Q water). The electrodes were connected to a constant current stimulation device (TCT Research 1 CH tDCS Model 101, Hong Kong), powered by two alkaline batteries (9v) with a maximum output of 2 mA. A constant electric current of 2 mA intensity was used for 20 min. In the first 30 s of ramping, the current is slowly increased to the desired level, then the stimulator maintains the stimulation current constant and during the last two seconds, the current is automatically reduced to avoid electric shock and visual flash. Volunteers were informed about possible discomforts and instructed to communicate if the discomfort was unsustainable.

Sham tDCS protocol

The sham tDCS protocol followed the protocol described above for active tDCS, however after the initial 30 s of ramp, the stimulator was turned off.

AE protocol

In their entirety, the subjects who made up the sample of the present study were classified using the International Physical Activity Questionnaire (IPAQ) as irregularly active B (those who did not meet any of the recommendation criteria regarding the frequency or duration of PE) or as sedentary (those who did not perform any PE for at least 10 continuous minutes during the week).

The members of the AE groups were subjected to walking on an ergometric treadmill (Movement Technology Treadmill electronic, Brazil) at a moderate intensity (40 to 59% of the reserve HR), and motivated through verbal stimuli to maintain the intensity at around 55% of the reserve HR. Fox's formula[34] HRmax = 220-age was used to estimate HRmax, and its result was individually applied to the formula for prescribing the PE intensity recommended by ACSM[35]: desired HR= [(HRmax/peak – HRrest) × % of desired intensity] + HRrest.

The AE sessions were performed over five consecutive days and lasted 40 min each, divided into three moments: warm-up (5 min), conditioning (30 min) and calming down (5 min). To monitor individual effort intensity during PE, a Polar heart rate monitor was used. This protocol is in line with the ACSM[35] guidelines for PE prescription and was performed equally in all training sessions.

Statistical analysis

The Graph pad Prism statistical package version 6.0 was used for data analysis. Data normality and homogeneity of variances were tested by Kolmogorov-Smirnov and Bartlett test, respectively. Differences in changes between moments (pre-test x post-test) in the groups' continuous variables were verified using the paired Student's t-test or the Wilcoxon test for variables that showed an asymmetric distribution. To make comparisons between the groups G1 (tDCS), G2 (AE), G3 (tDCS + AE) and G4 (tDCS Sham + AE) in each variable, including the frequency of alpha and gamma in the pre-and post-test moments, we used the one-way ANOVA (normal distribution) or the Kruskal-Wallis test (variables with asymmetric distribution), with Bonferroni's post hoc test when appropriate. A simple linear regression was performed to model the change in the number of cigarettes smoked over time (daily cigarette consumption x time). The mean and standard deviation were used to describe the sample characteristics. The results were considered significant when $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Results

In the pre-moment, the four groups (tDCS, AE, tDCS + AE and sham tDCS + AE) did not differ concerning the variables CO levels, MCSB, craving levels and alpha and gamma activity in the LA, RA, LP and RP region during the EEG ($p > 0.05$ for all tests). Nicotine dependence measured by Fagerström was estimated to be high or very high in ten (24.3%) of smokers (Fagerström score ≥ 6), moderate in twenty-two (53.6%), (Fagerström score = 5) and low in nine (22.1%), (Fagerström score = 3).

	tDCS (G1) $n=10$		AE (G2) $n=9$		tDCS + AE (G3) $n=12$		Sham tDCS + AE (G4) $n=10$	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Level of CO in exhaled breath (ppm)	20.2 ± 7.5	16.3 ± 6.7	14.2 ± 9.3	8.0 ± 6.2*	22 ± 10.9	13.6 ± 7.5**	21.8 ± 10.9	15.6 ± 9.6*
Motivation to change smoking behavior	9.5 ± 1.3	9.9 ± 0.8	9.4 ± 1.2	9.6 ± 1.1	9.5 ± 0.7	10.4 ± 1.0**	9.8 ± 0.9	11.4 ± 1.3**
Craving level	33.4 ± 14.1	30.5 ± 16.1*	26.6 ± 13.2	24.6 ± 11.0	43.1 ± 15.6	21.4 ± 10.8**	35.2 ± 17.2	26.8 ± 13.8

Table 1. Pre and post tests of variables level of CO, motivation to change smoking behavior and craving level for G1 to G4 groups. *$p < 0.05$ **$p < 0.01$.

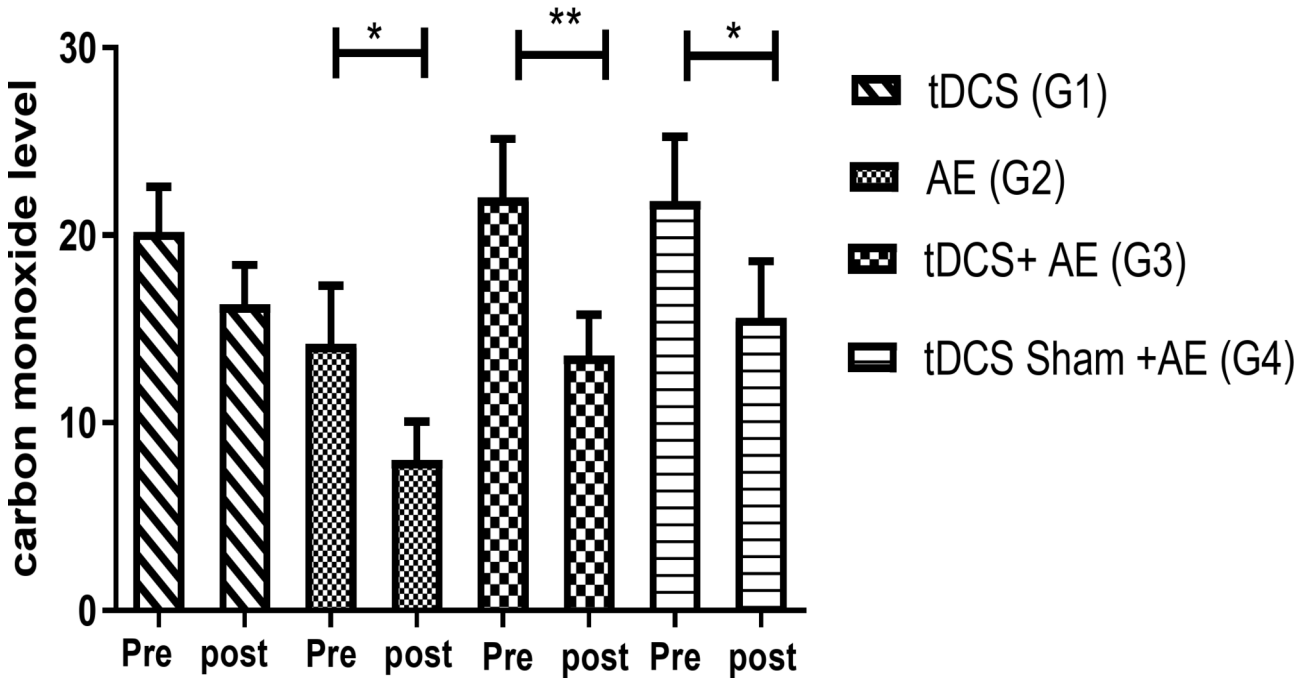

Fig. 1. Carbon monoxide (CO) levels (mean ± standard error). *$p < 0.05$, **$p < 0.01$. There was no significant difference between the groups.

CO levels

The CO level at the end of treatment showed a significant decrease in the three groups that performed AE alone or combined with tDCS when compared to the initial moment (Table 1). The G2 group decreased by 56.3% ($T = 2.65$; $df = 8$; $p = 0.02$; $\eta^2 = 0.46$), G3 decreased by 61.3% ($p = 0.003$; $W = 75$) and G4 decreased by 71.5% ($T = 2.69$; $df = 9$; $p = 0.02$; $\eta^2 = 0.44$) (Fig. 1). Although G1 did not show a significant drop, there was a reduction of 19.4% at the end of the intervention. There was no significant variation when comparing the type of intervention and treatment time between the groups.

Motivation to change smoking behaviour (MCSB)

As shown in Table 1; Fig. 2, the MMCF at the end of treatment showed a significant increase in groups G3 (15.7%) ($T = 3.02$; $df = 11$; $p = 0.01$; $\eta^2 = 0.45$) and G4 (15.9%) ($T = 3.83$; $df = 9$; $p = 0.004$; $\eta^2 = 0.62$) concerning the initial period. There was a small increase in motivational change in group G1 (4.1%) and group G2 (2.2%), but they did not reach significant differences. There was no significant variation when comparing the type of intervention and treatment time between the groups.

Craving level

Craving at the end of treatment showed a significant decrease only in the G3 group (tDCS + AE) with a reduction of 50.4% ($T = 5.00$; $df = 11$; $p = 0.0004$; $\eta^2 = 0.69$). Groups G1 (tDCS), G2 (AE) and G4 (tDCS Sham + AE), despite not showing a significant reduction, showed reductions of 9.3%, 8.9% and 23.8%, respectively (Table 1). There was no significant variation when comparing the type of intervention and treatment time between the different groups (Fig. 3).

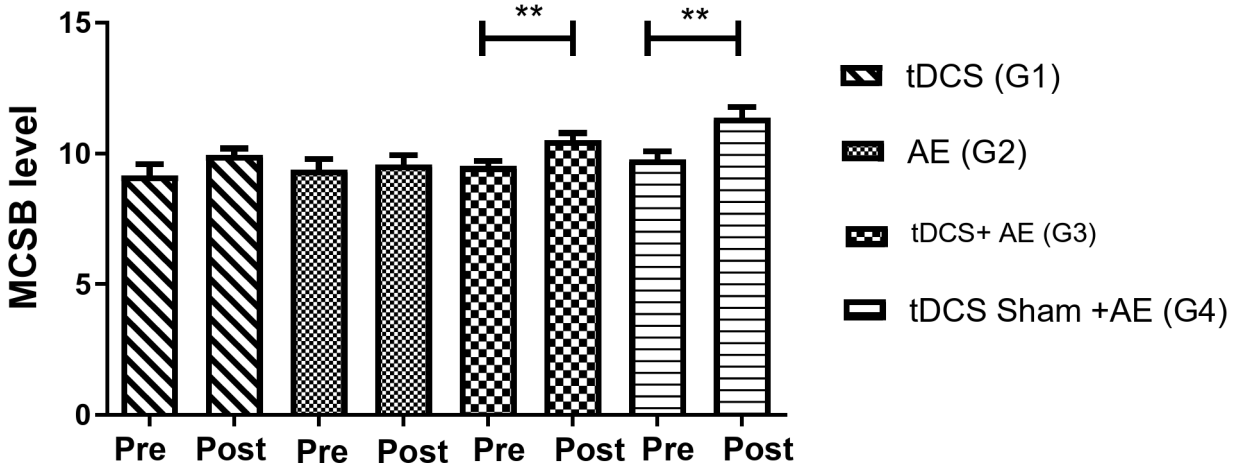

Fig. 2. Cigarette consumption in the groups. ***$p < 0.001$ and *$p < 0.05$.

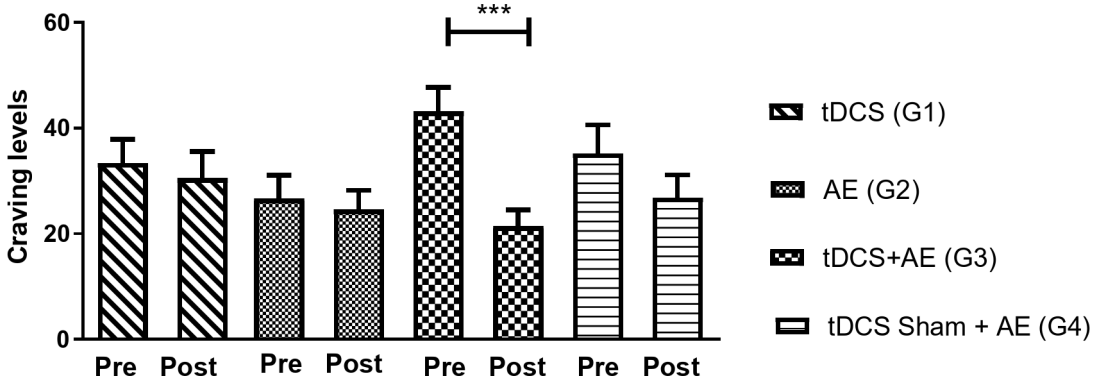

Fig. 3. MMCF level (mean ± standard error) **$p < 0.01$.

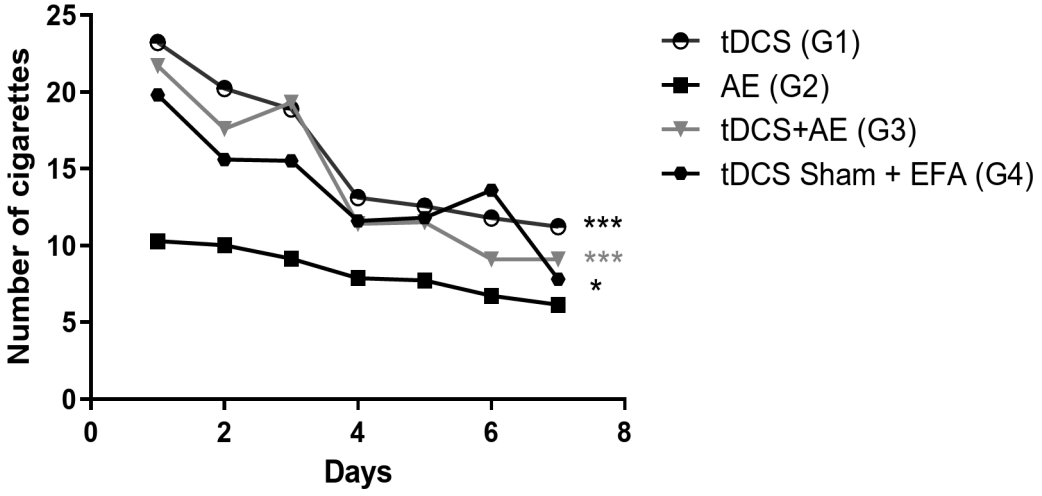

Fig. 4. Craving level (mean ± standard error) ***$p < 0.001$.

Cigarette consumption

For daily cigarette consumption, a linear regression was performed, which showed that only G2 did not show a significant decrease in cigarette consumption over time (Fig. 4). There was no significant difference between the groups.

EEG/alpha rhythm recordings

No significant differences were found in the alpha rhythm at times of cigarette exposure in any of the groups (Table 2).

EEG recordings/gamma rhythm

About the gamma rhythm, group G1 showed a significant increase in the left anterior (LA) ($T = 2.46$; $df = 9$; $p = 0.03$; $\eta^2 = 0.40$) and left posterior (LP) ($T = 2.90$; $df = 9$; $p = 0.01$; $\eta^2 = 0.48$) regions during task 1 (video) (Table 3; Figs. 5 and 6, respectively). A similar increase was also observed in the right anterior region (RA) ($p = 0.01$; $W = -36$) at the time of task 2 (cigarette handling) (Fig. 7). A significant increase in the gamma rhythm was also observed in the G4 group during task 1 (video) in the left anterior (LA) ($p = 0.04$; $W = -25$) and right posterior (RP) ($p = 0.04$; $W = -30$) regions (Figs. 8 and 9, respectively). Additionally, we found a significant difference in the decrease in gamma waves between groups G1 and G3 ($p < 0.05$) in the RA region during task 2

Pre				Post			
G1—tDCS (n = 10)							
CE—closed eyes							
LA	RA	LP	RP	LA	RA	LP**	RP
9.01 ± 1.0	9.19 ± 0.9	9.47 ± 0.8	8.94 ± 0.9	9.05 ± 0.8	8.81 ± 1.0	8.72 ± 0.6	8.79 ± 0.7
T1- video							
LA	RA	LP	RP	LA	RA	LP	RP
9.07 ± 1.2	9.55 ± 1.69	9.29 ± 1.2	9.08 ± 1.2	9.14 ± 0.9	9.44 + ± 1.2	9.5 ± 0.9	9.22 ± 1.5
T2—manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
9.37 ± 1.0	9.66 ± 1.4	8.69 ± 0.8	9.57 ± 1.3	8.87 ± 0.9	9.16 ± 0.9	9.12 ± 0.8	9.19 ± 0.9
G2—AE (n = 9)							
CE—closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP**
9.38 ± 0.7	9.7 ± 1.1	9.55 ± 0.8	9.38 ± 0.9	9.5 ± 0.9	9.11 ± 0.6	9 ± 0.7	8.94 ± 0.8
T1—video							
LA	RA	LP	RP	LA	RA	LP	RP
9.66 ± 0.8	9.44 ± 1.0	9.83 ± 0.8	9.77 ± 1.0	9.66 ± 1.1	9.11 ± 0.7	9.61 ± 0.9	9.33 ± 0.8
T2—manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
9.61 ± 0.9	9.5 ± 0.9	9.61 ± 1.2	10.27 ± 1.1	9.55 ± 0.7	9.77 ± 1.2	9.72 ± 1.3	9.55 ± 0.9
G3—tDCS + AE (n = 12)							
CE—closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP
8.94 ± 1.0	9.18 ± 1.4	9.26 ± 1.0	8.81 ± 0.8	9.36 ± 0.9	9.39 ± 1.1	9.05 ± 0.7	9.36 ± 1.0
T1—video							
LA	RA	LP	RP	LA	RA	LP	RP
9.60 ± 0.9	9.26 ± 0.8	8.92 ± 0.8	9 ± 0.7	9.63 ± 1.1	9.26 ± 1.1	9.28 ± 0.8	9.10 ± 1.0
T2—manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
9.44 ± 1.2	9.52 ± 1.3	9.60 ± 1.2	9.42 ± 1.2	9.78 ± 1.1	9.39 ± 1.4	9.13 ± 0.8	9.18 ± 0.9
G4—sham tDCS + AE (n = 10)							
CE—closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP
9.45 ± 0.7	8.6 ± 0.8	9.2 ± 0.5	8.75 ± 0.8	9.4 ± 0.8	9.3 ± 0.8	9.1 ± 0.9	9.15 ± 1.0
T1—video							
LA	RA	LP	RP	LA	RA	LP	RP
9.6 ± 1.2	8.65 ± 0.8	8.9 ± 0.9	8.95 ± 0.8	9.85 ± 1.3	9.35 ± 1.3	9.15 ± 1.2	9.35 ± 1.0
T2—manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
9.3 ± 0.9	9.55 ± 1.5	9.15 ± 1.0	9.15 ± 0.8	9.65 ± 1.2	9.6 ± 0.9	9.5 ± 1.2	9.15 ± 1.0

Table 2. Mean ± standard deviation of the power of the alpha rhythm in the left anterior (LA), right anterior (RA), left posterior (LP) and right posterior (RP) quadrants, at the closed eyes (CE), T1 and T2 moments, of the G1, G2, G3 and G4 groups in the pre- and post test time. **P < 0.01, pre and post test comparison.

Pre				Post			
G1 – tDCS ($n=10$)							
CE – closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP
23.23 ± 0.3	23.71 ± 1.0	23.4 ± 0.7	23.52 ± 0.5	23.53 ± 0.8	24.02 ± 1.6	23.9 ± 1.6	24 ± 1.5
T1 - video							
LA	RA	LP	RP	LA*	RA	LP**	RP
23.44 ± 0.5	23.52 ± 0.6	23.51 ± 0.6	23.57 ± 0.8	24.09 ± 1.1	24.38 ± 1.6	24.65 ± 1.5	24.58 ± 1.6
T2 – manipulation							
LA	RA	LP	RP	LA	RA**	LP	RP
23.58 ± 0.8	23.4 ± 0.5	23.34 ± 0.3	23.8 ± 0.9	24.14 ± 1.4	24.74 ± 2.0	24.46 ± 1.8	24.69 ± 2.0
G2 – AE ($n=9$)							
CE – closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP
23.42 ± 0.7	23.34 ± 0.1	23.48 ± 0.6	23.83 ± 1.1	23.76 ± 0.9	23.7 ± 0.9	23.7 ± 1.1	23.86 ± 1.0
T1 – video							
LA	RA	LP	RP	LA	RA	LP	RP
23.36 ± 0.4	23.07 ± 0.0	23.42 ± 0.2	23.58 ± 0.5	23.67 ± 0.9	23.48 ± 0.6	23.65 ± 0.9	23.53 ± 0.5
DP = 0.46	0.06	0.27	0.52	0.96	0.59	0.93	0.54
T2-Manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
23.21 ± 0.2	23.26 ± 0.3	23.45 ± 0.6	23.59 ± 0.6	23.61 ± 0.7	23.21 ± 0.2	23.45 ± 0.5	23.20 ± 0.2
G3 – tDCS + AE ($n=12$)							
CE – closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP
24.15 ± 1.7	24.07 ± 1.6	24.01 ± 1.3	24.29 ± 1.7	23.6 ± 1.3	23.64 ± 1.3	23.73 ± 0.8	24.05 ± 1.6
T1 – video							
LA	RA	LP	RP	LA	RA	LP	RP
24.31 ± 1.6	24.25 ± 1.7	24.08 ± 1.7	24.28 ± 1.7	23.51 ± 0.8	23.67 ± 1.3	23.84 ± 1.0	24.03 ± 1.4
T2 – manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
23.97 ± 1.6	24.03 ± 1.6	24.07 ± 1.4	24.10 ± 1.6	23.74 ± 1.2	23.65 ± 1.3	23.91 ± 1.3	23.8 ± 1.4
G4 – sham tDCS + AE ($n=10$)							
CE – closed eyes							
LA	RA	LP	RP	LA	RA	LP	RP
23.28 ± 0.3	23.43 ± 0.5	23.4 ± 0.4	23.41 ± 0.5	23.19 ± 0.2	23.29 ± 0.2	23.62 ± 0.6	23.20 ± 0.1
T1 – video							
LA	RA	LP	RP	LA*	RA	LP	RP*
23.14 ± 0.1	23.15 ± 0.1	23.26 ± 0.2	23.24 ± 0.2	23.55 ± 0.5	23.55 ± 0.6	23.69 ± 0.6	23.62 ± 0.5
T2 – manipulation							
LA	RA	LP	RP	LA	RA	LP	RP
23.21 ± 0.2	23.24 ± 0.4	23.34 ± 0.4	23.12 ± 0.1	23.15 ± 0.1	23.34 ± 0.4	23.3 ± 0.3	23.46 ± 0.7

Table 3. Mean ± standard deviation of the power of the gamma rhythm in the left anterior (LA), right anterior (RA), left posterior (LP) and right posterior (RP) quadrants, at the closed eyes (CE), T1 and T2 moments, of the G1, G2, G3 and G4 groups in the pre- and post test time. *$p < 0.05$ and **$p < 0.01$, pre and post test comparison.

(Fig. 10). In Figs. 11, 12, 13 and 14, representative images of the gamma rhythm in the different groups can be seen.

Discussion

The results of the present study demonstrated that tDCS associated with AE (G3) significantly reduced cigarette consumption and craving, in addition to significantly increasing MCSB. These results were accompanied by a significant decrease in gamma rhythm power during exposure to cigarette signals. On the other hand, the increased activation of gamma rhythm power in the EEG observed during cigarette exposure in groups G1 and G4 did not generate a decrease in craving. These findings demonstrate that active tDCS when associated with AE was effective in promoting a reduction in craving, cigarette consumption and CR during exposure to cigarette signs.

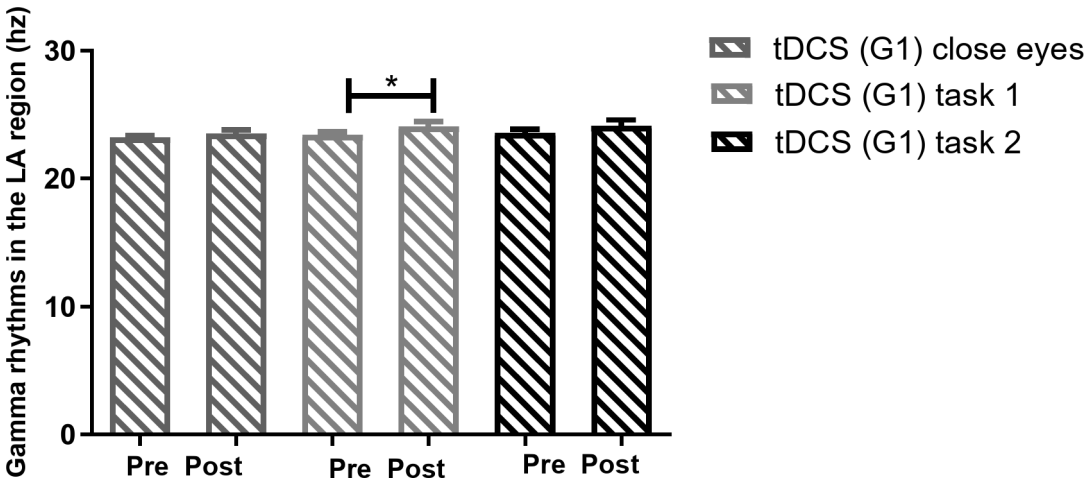

Fig. 5. Gamma rhythm of the left anterior region (LA) (mean ± standard error) $^{*}p < 0.05$.

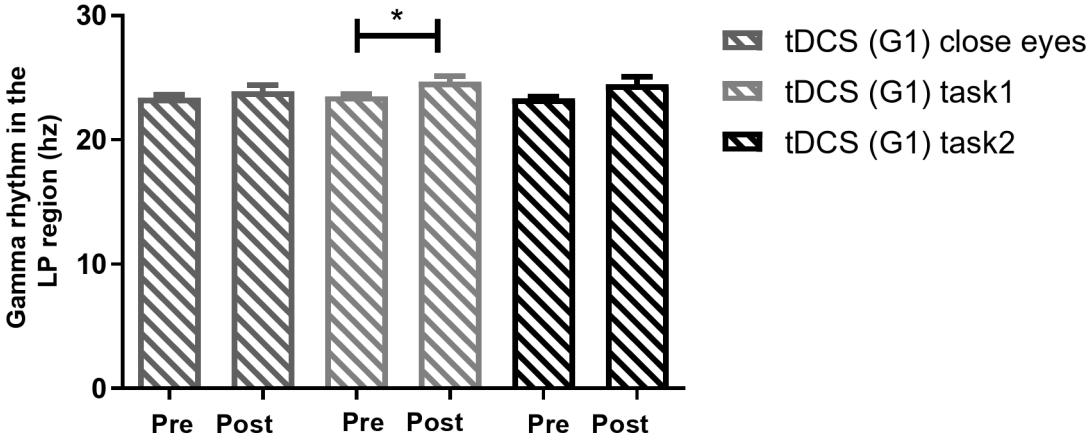

Fig. 6. Gamma rhythm of the left posterior region (LP) (mean ± standard error) $^{*}p < 0.05$.

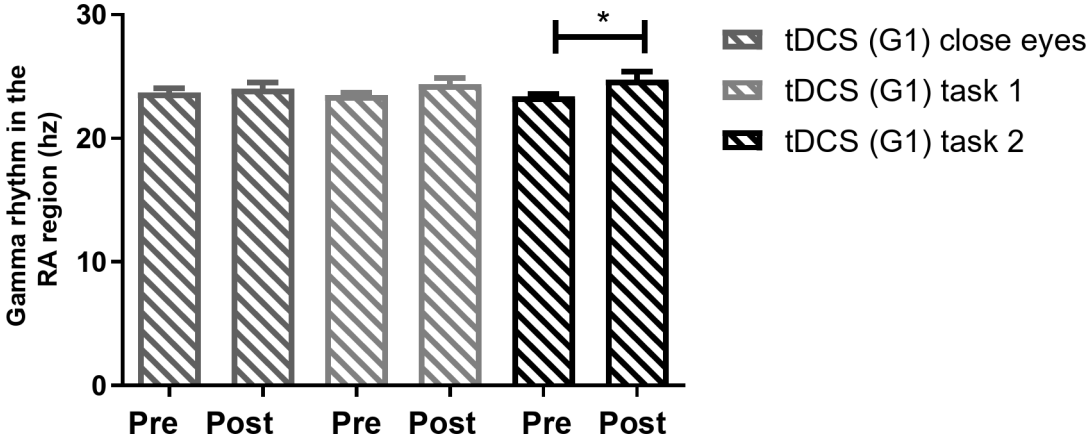

Fig. 7. Gamma rhythm of the right anterior region (RA) (mean ± standard error) $^{*}p < 0.05$.

The results of the CO measurements used to verify smoking status and monitor cigarette consumption over the five days of intervention demonstrated a significant decrease in CO levels in the 3 groups that performed AE, whether isolated or combined with tDCS. This result was already expected, since when subjects are exposed to PE they increase the elimination of CO[36,37]), reinforcing once again the importance of PE in the treatment

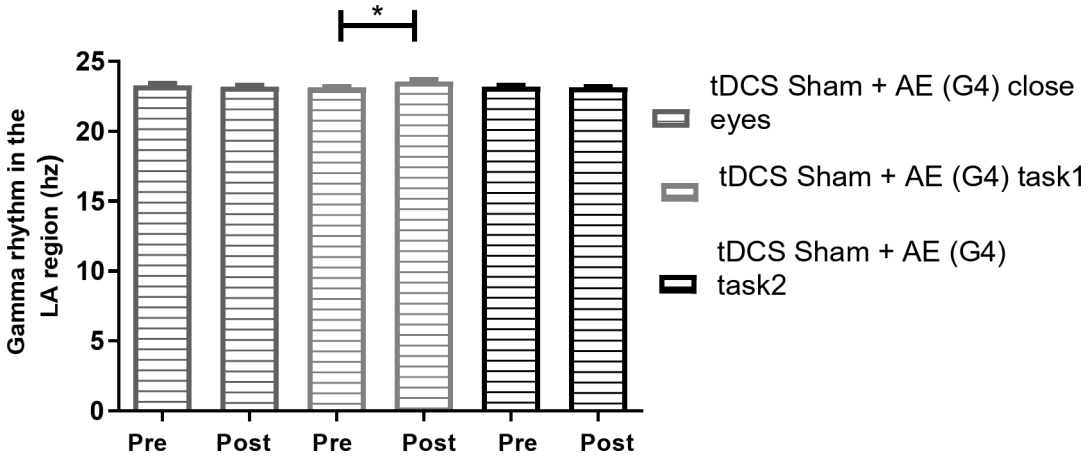

Fig. 8. Gamma rhythm of the left anterior region (LA) (Mean ± standard error) $^{*}p < 0.05$.

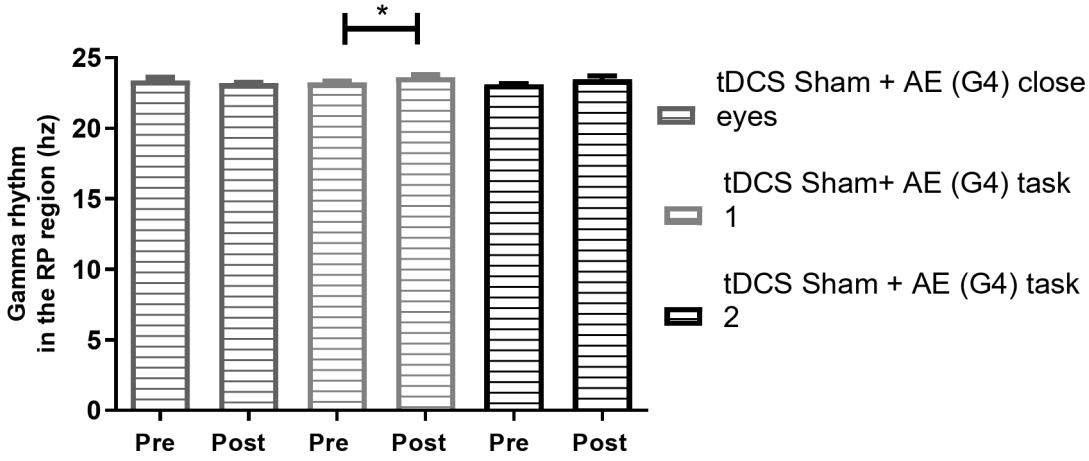

Fig. 9. Gamma rhythm of the right posterior region (RP) (mean ± standard error) $^{*}p < 0.05$.

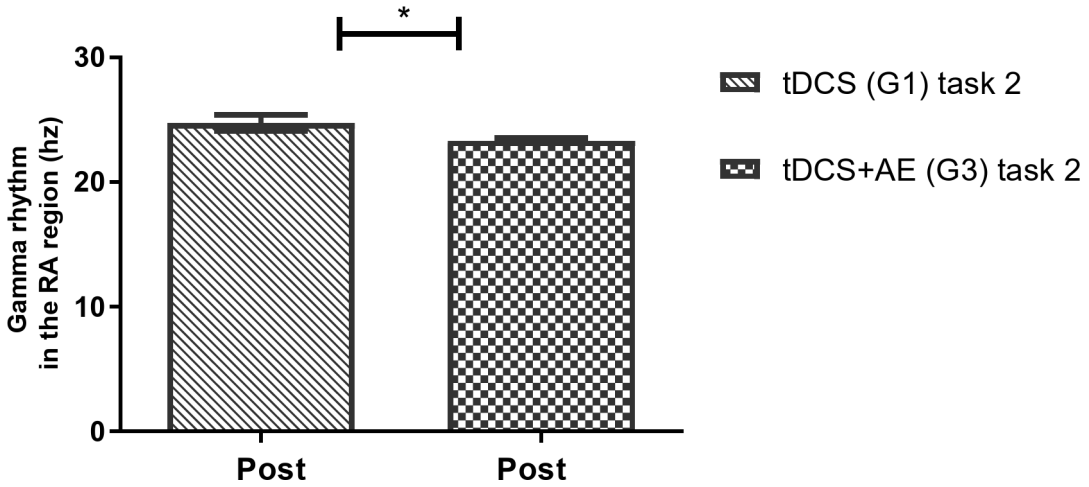

Fig. 10. Gamma rhythm of the right anterior region (RA) during the post-test of task 2 (mean ± standard error) $^{*}p < 0.05$.

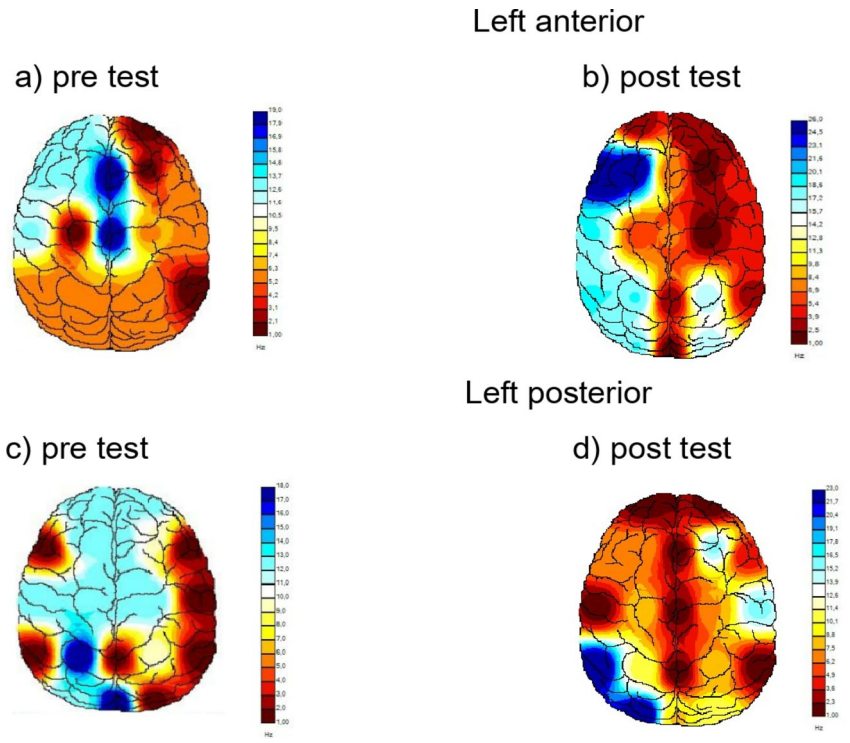

Fig. 11. Recording of increased gamma activity during task 1, in group G1 (tDCS), in the left anterior (**a**,**b**) and posterior (**c**,**d**) regions pre and post test. Color scale bar represents brain waves frequency (Hz). The colors of the spectrum are distinguished by the different frequency ranges from low (red) to high (blue) : delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ). Dark blue shows an increase in gamma activity.

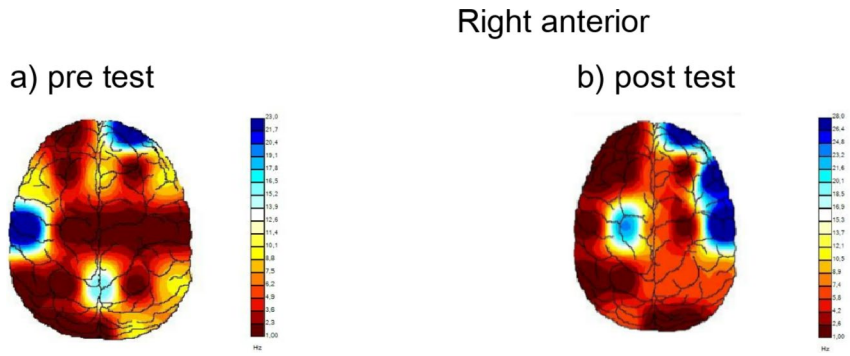

Fig. 12. Recording of increased gamma activity during task 2, in group G1 (tDCS), in the right anterior region pre (**a**) and post test (**b**). Color scale bar represents brain waves frequency (Hz). The colors of the spectrum are distinguished by the different frequency ranges from low (red) to high (blue) : delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ). Dark blue shows an increase in gamma activity.

of smokers. Blumenthal[38] recalls that the central problem of the presence of CO above the acceptable level in the body comes from the fact that the affinity of CO with hemoglobin is approximately 200 to 250 times greater than that of O2. Therefore, CO has great potential to alter the transport of O2 in the blood, as it competes with O2 for the binding site on the hemoglobin molecule, as well as reducing the release of O2 from hemoglobin to the tissues[39].

It was observed that the G2 group did not significantly reduce self-reported cigarette consumption during the intervention period. This may have occurred because, in general, the sample that participated in the research was more interested in tDCS than in AE, which may have interfered with the motivation to reduce cigarette consumption in G2. Since tDCS is a technique that is little known by the population in clinical practice, this factor may have produced greater interest among participants, to the detriment of physical exercise, which is already a widely known practice, although a large part of the population does not enjoy its benefits because they do not have an active lifestyle[40]. Thus, these factors may have led to a bias in the motivation of the recruited groups,

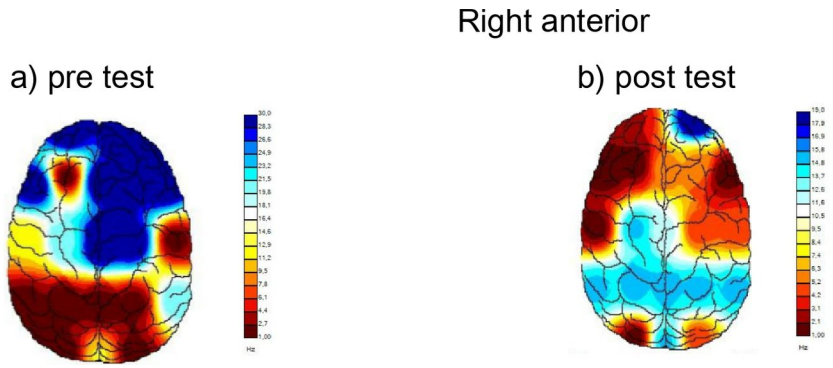

Fig. 13. Recording of decreased gamma activity in G3 (tDCS + AE) group (**b**) in the right anterior region during task 2 compared to G1 (tDCS) group (**a**). Color scale bar represents brain waves frequency (Hz). The colors of the spectrum are distinguished by the different frequency ranges from low (red) to high (blue): delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ). Dark blue shows an increase in gamma activity.

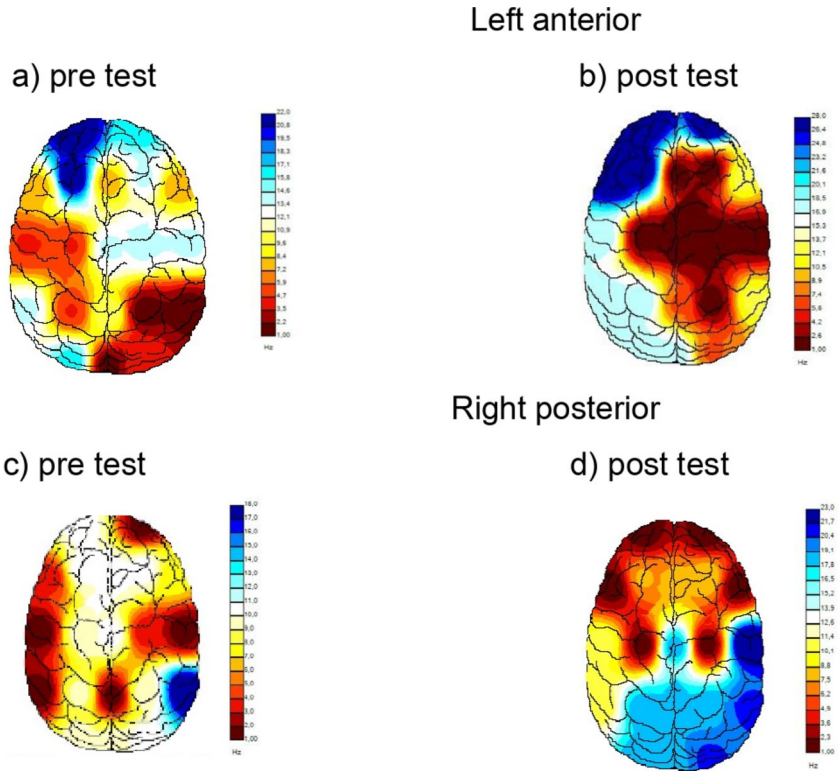

Fig. 14. Recording of increased gamma activity during task 1, in group G4 (sham), in the left anterior (**a**,**b**) and right posterior (**c**,**d**) regions pre and post test. Color scale bar represents brain waves frequency (Hz). The colors of the spectrum are distinguished by the different frequency ranges from low (red) to high (blue) : delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ). Dark blue shows an increase in gamma activity.

since as demonstrated by Vangeli et al.[41], motivation increases the chance of reducing cigarette consumption in smokers.

Regarding CO levels, it was observed that only G1 did not show a reduction in this variable. Although it has been demonstrated that tDCS can reduce CO concentration among smokers[42], this was not observed in the present study. This finding may partly be related to the heterogeneity in cigarette consumption levels, as Borgne-Krams et al.[43] reported that tDCS reduced CO levels in heavy smokers (more than 20 cigarettes per day), but not in moderate smokers. Therefore, the heterogeneity of the sample in the present study may account for the observed results. Additionally, the presence of exercise in groups G2 to G4 may have contributed to the reduction in CO levels, as all groups that performed aerobic exercise showed a decrease in this variable. This reinforces the importance of combining tDCS with physical exercise for better outcomes in the studied population. Furthermore, it is also possible to hypothesize that the decrease in CO levels in G3 and G4 was

due to both lower cigarette consumption and enhanced CO elimination following exercise. It is important to consider that G2 was the group with the lowest *n*compared to the others, due to lower adherence by volunteers, and started with a lower cigarette consumption than the others. This lower initial consumption by volunteers may be due to the characteristics of the participants who made up this group since most of them were employees of the university where the data collection took place. It is well known that the level of education affects adherence and consumption of cigarettes[44].

Although there appears to be no consensus in the literature on the effects of PE on smoking cessation, some studies have found that a smoking cessation program based on PE incentives was highly effective in reducing short-term cigarette consumption[45] and in improving long-term smoke-free maintenance[46]. Additionally, Park et al.[47] state that regular participation in PE programs can mitigate the adverse effects of smoking on the vasculature, reducing the chances of the emergence of cardiovascular comorbidities. Furthermore, greater cardiorespiratory fitness is associated with a lower risk of lung cancer incidence in former smokers and a lower risk of cancer mortality in current smokers who have been diagnosed with lung cancer[48]. Therefore, regular participation in PE is recommended to mitigate the adverse health effects of smoking.

The findings of the present study also bring a component that demonstrates the importance of EFA being integrated into treatment strategies for smokers and MCSB, as it was observed that when AE was not isolated, but associated with active or sham tDCS, it significantly increased MMCF about the initial period. Blank et al.[49] corroborate these results and Vangeli et al.[41] complement that the MCSB and the reduction in cigarette consumption is a two-way street, since the reduction in smoking can increase the MCSB and that motivation is highly predictive of attempts to quit, reduce smoking dependence and success in abandonment.

Regarding the level of craving, only G3 group showed a significant decrease. These results corroborate other studies that used tDCS with PE in the clinical setting on pain patients improvement[50], Parkinson's disease[51], and motor sequelae after a stroke[52], among others[53]. This combination of interventions has gained increasing prominence in the scientific community, so recent articles of systematic reviews and meta-analyses have addressed the subject, presenting favourable results[54] and encouraging more research for the use of tDCS in combination with AE[55] in different contexts, including addiction[20].

Regarding CR to cigarette cues recorded by EEG, some previous studies explored experimental CR protocols with cigarette cues in smokers, with results indicating that CR to smoking cues is a central feature of nicotine dependence and is associated with an increase in subjective desire[24]and can predict relapse vulnerability[26]. Therefore, there is support for evidence of a causal relationship between cue reactivity and immediate smoking.

In the EEG/alpha rhythm recordings, no significant differences were found in the moments of exposure to cigarettes in any of the groups. Among other functions, alpha waves measure the deactivation of the cortical area, which may indicate that the frontal regions are being used less during cigarette exposure. However, in the present study, the alpha rhythm was not altered, which, in a certain way, is consistent with the results we expected since the major concern of different approaches to smoking cessation would be to maintain or not reduce alpha waves in the PFC at the time of exposure to cigarettes.

About the gamma rhythm, the G1 group showed a significant increase in the LE and LP regions during task 1 (video) and in the RA region at the time of task 2 (cigarette manipulation). The G4 group also showed a significant increase during task 1 (video) in the LA and RP regions. The G3 group was the only one to show a tendency towards a decrease in CR during the moment of cigarette exposure and to show a significant difference in the decrease in gamma waves between the G1 and G3 groups. These results support the hypothesis presented in the present study, that active tDCS associated with AE decreases CR at cigarette signals and consequently reduces craving. Several studies are in line with our findings, such as the study by Allenby et al.[56], demonstrating that participants who showed greater CR to the suggestion of smoking in the anterior cingulate cortex during acute abstinence (compared to smoking satiety) were more likely to relapse. Additionally, greater abstinence-induced change in anterior cingulate cortex activation also predicted fewer total days of abstinence. Furthermore, Bu et al.[57] reiterate that reducing CR to cigarette signs has the potential to improve smoking cessation outcomes.

In turn, McClernon et al.[18] evaluated smokers' exposure to personal environments related to smoking on activation in the hippocampus and other areas of the brain involved in conditioned reward. The results revealed an increase in CR in the hippocampus and insula, concomitant with intense craving, followed by smoking behaviour. Mondino et al.[6], hypothesized that active tDCS would reduce CR to smoking cues, especially in prefrontal structures, however, they found an increase in CR to smoking cues. The authors justified their results based on the assumption that the increase in CR in the PFC could reflect a strategy of resisting desire. In the findings of the present study, CR did not reflect a reduction in craving, but rather in cigarette consumption, however, these results were not different from placebo. Although the results of the present study represent more acute findings, it is important to make some considerations regarding long-term smoking cessation, as this is one of the goals of clinical studies like ours. The process of quitting smoking involves physical, psychological, and social challenges that do not disappear quickly, and maintaining abstinence over time is often the most difficult aspect of treatment. Psychological factors, such as stress, anxiety, and depression, are often triggers for relapse, as are social situations or environments where smoking was habitual[58]. Other factors, such as lack of social support, and limited access to long-term interventions, also contribute to relapse[58]. Studies on smoking cessation show that long-term relapse rates are remarkably high, even with supportive therapies and pharmacological treatments. On average, about 50–60% of individuals relapse within the first year after quitting smoking. For example, in Zhang et al.'s study[59], the likelihood of relapse decreased as the duration of abstinence increased, with rates of 49%, 20%, and 6.63% at 2, 4, and 8 years of abstinence, respectively. Therefore, if interventions like those applied in the present study are maintained for longer periods, they can be effective auxiliary tools in smoking cessation treatment, both with tDCS, reducing cigarette consumption and craving, and with physical exercise, which, as discussed earlier, can minimize the adverse health effects of smoking.

Some studies using sham groups observed some positive effects regarding cigarette consumption and MCSB. First, it is necessary to consider that in groups receiving a placebo, the mere act of participating in the experiment, combined with the motivation and expectation of improvement or the belief that they are receiving treatment, may generate subjective and even to some extent objective changes. However, evidence from Lasogga et al.[60] meta-analysis study comparing response inhibition between active and sham tDCS showed no difference in variances between active and sham tDCS conditions, which reinforce our findings for tDCS active in craving reduction.

Thus, the occurrence of placebo effects in sham groups is, to some extent, an expected and controlled variable, which was appropriately considered in the study design. Additionally, Mondino et al.[6] report that the use of a parallel design may contribute to a stronger placebo effect compared to previous studies that used a crossover design. This can be seen in the meta-analysis by Dollfus et al.[61] in which, investigating the impact of study design on the placebo effect in non-invasive brain stimulation studies, revealed a significant placebo effect in parallel studies, but not in crossover studies.

Finally, no serious adverse effects were reported by the volunteers during the tDCS sessions, only reports of tingling sensations, redness, dizziness and, less frequently, headache, and discomforts that are already well described in the literature.

Limitations

Some important limitations were observed in the present study. First, despite the strong general correlation between self-reported cigarette consumption described by previous studies and the CO test, nicotine addiction was not proven by urine testing, which is one of the gold standard measures to assess intoxication. Furthermore, although the EEG exam was performed in 2 standardized time windows, a small part was collected in different shifts, which may have caused some interference with our results. Additionally, we used the tDCS montage focusing on the PFC and the insula, however, due to its limited spatial depth and its non-focal nature, we do not know whether the stimulation reached the target or which part of the insula received the stimulus. Another possible limitation associated with the present study is the small number of intervention sessions, which limits knowledge about the outcome of a long-term intervention.

A potential source of bias was the sample size. However, we estimate that although the analyses were performed with 41 volunteers, which is below the calculated sample size, this number is consistent with other studies that used similar sample sizes and found reliable results[4,6,62,63].

Likewise, studies performed by Fecteau et al.[62] and Fregni et al.[4], have found beneficial effect of tDCS for reducing addictive behaviors, enrolling 12 and 24 volunteers per group, respectively, which is similar to our sample size. Furthermore, the total sample enrolled among experimental designs can vary according to different methodological approaches. For instance, Boggio et al.[6,63] had two groups of participants, unlike our study, which involved four groups of participants.

The number of groups, combined with the several experimental sessions, required greater commitment from the volunteers (more time, more data collection sessions, or even specific conditions to participate), making the sampling more restrictive and limiting the number of available volunteers.

Randomization in clinical trials is one of the most used techniques to compare groups of people who have received different treatments[64]. However, special attention is necessary to avoid biases during selection of participants as in ongoing recruitment, as used in our study, can lead to reduced sample power.

In this sense, future research with a larger number of participants and tDCS sessions, observing the time and intensity of stimulation would be very useful for tDCS + AE implementation in clinical practice.

Conclusions

In conclusion, the present study demonstrated that active tDCS, when associated with AE, was effective in promoting a reduction in craving, cigarette consumption and CR during exposure to smoke signals, and could become a complementary clinical tool in the treatment of smoking.

Data availability

Data will be made available upon request. Contact aximenes@ccbi.ufal.br.

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Author contributions

Author contributionsG.A.S., L.C.S, E.M.T.F and A.X.S designed the experiment., G.A.S and K.M.S. performed the experiment. G.A.S., L.C.S, E.M.T.F and A.X.S. analyzed the data and G.A.S., M.V.D., and A.X.S. wrote the manuscript. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics

This study was performed in accordance with the resolutions of the Brazilian National Health Council and approved by the Research Ethics Committee of the Federal University of Alagoas (UFAL), number 2.896.666 15/09/2018.

Informed consent

All volunteers were previously informed about the objectives of the study, as well as the possible risks, discomforts and benefits from their participation and received the Informed Consent Form to read it and sign it.

Additional information

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