Drug and Alcohol Dependence 214 (2020) 108152

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Eye tracking of smoking-related stimuli in tobacco use disorder: A proof-of-concept study combining attention bias modification with alpha-transcranial alternating current stimulation

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ARTICLE INFO

Keywords:
Smoking
Attentional bias
Eye tracking
Delay discounting
Drug cues
Craving
Noninvasive brain stimulation
Transcranial alternating current stimulation

ABSTRACT

Background: Tobacco use disorder (TUD) is characterized by the presence of an attentional bias (AB) towards smoking-related stimuli. We investigated whether combining an AB modification paradigm (ABM) with transcranial alternating current stimulation (tACS) applied over the dorsolateral prefrontal cortex (DLPFC) reduces the AB towards smoking-related stimuli, as well as craving level and impulsive choices.

Methods: In a sham-controlled, crossover preliminary study, 19 subjects with TUD received two stimulation arms: 1) active tACS (10 Hz, 2 mA, 30 min) combined with ABM and 2) sham tACS combined with ABM, in a randomized order, separated by one week. AB towards smoking cues during passive observation of smoking and neutral cues was assessed with an eye-tracking device and reactions times at a visual-probe task. Craving level was measured with the Questionnaire of Smoking Urges. Impulsive choices were assessed with the delay discounting task.

Results: Active tACS combined with ABM reduced the amount of time spent looking at smoking-related pictures ($p = 0.03$), prevented the increase of self-reported desire to smoke ($p = 0.026$), and reduced the proportion of impulsive choices ($p = 0.049$), compared to sham tACS combined with ABM. No significant effects were reported on other craving dimensions and on AB based on reaction times.

Conclusions: These preliminary findings suggest that combining tACS with ABM may help smokers who wish to quit by reducing the desire to smoke, attention to smoking-cues, and impulsive decision-making.

1. Introduction

Substance use disorders (SUD), including tobacco use disorder (TUD), are characterized by biased cognitive processes (Rooke et al., 2008), high impulsivity (Verdejo-García et al., 2008) and impaired decision-making (Ekhtiari et al., 2017). More specifically, individuals with SUD display an attentional bias (AB), which can be defined as the preferential allocation of attention resources to substance-related stimuli with difficulty in disengaging from these stimuli (Field and Cox, 2008). Remarkably, the AB appears to be present in almost every known abused substance such as tobacco, alcohol, cannabis, cocaine and opiates (Field and Cox, 2008). The AB is also suggested to play a significant role in craving (e.g., Manchery et al., 2017; for a metaanalysis see Field et al., 2009b), relapse, and poorer treatment outcomes in individuals with SUD (Garland et al., 2012; Marissen et al., 2006; Powell et al., 2010; Waters et al., 2003, but see also Christiansen et al., 2015b).

According to the supposed clinical relevance of AB, a growing number of methods have been developed to reduce AB with the goal of decreasing SUD symptoms. One of these methods is attention bias modification (ABM). ABM consists in training attention away from substance-related cues, typically by using modified versions of the visual-probe tasks commonly used to investigate AB. Visual-probe tasks usually involve presenting pairs of stimuli: one neutral and one substance-related stimuli side by side and then having a probe to replace one of the stimuli with equal frequency. Participants are asked to identify the probe as quickly as possible. In ABM paradigms, the visual-probe task is modified such as the probe replaces the neutral stimuli 100 % (or nearly) of the time. This method has shown promise in several clinical populations. For instance, training the attention away from threatening stimuli has been shown to decrease symptoms of anxiety in high-anxious individuals (Mogg et al., 2017).

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https://doi.org/10.1016/j.drugalcdep.2020.108152
Received 9 March 2020; Received in revised form 29 May 2020; Accepted 26 June 2020
Available online 02 July 2020
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In SUD, however, the effects of ABM seem less consistent (Cristea et al., 2016). For instance, in TUD, some studies showed that ABM can reduce the AB towards smoking cues (Attwood et al., 2008; Field et al., 2009a; Kerst and Waters, 2014; Lopes et al., 2014; Robinson et al., 2017), whereas some others found no effect on AB (Begh et al., 2015; Elfeddali et al., 2016; McHugh et al., 2010). Regarding smoking, only one study reported an effect on craving (Kerst and Waters, 2014), whereas most of the studies reported null findings on craving (Begh et al., 2015; Field et al., 2009a; McHugh et al., 2010; Robinson et al., 2017), tobacco seeking (Field et al., 2009a), and consumption (Begh et al., 2015; Lopes et al., 2014; Robinson et al., 2017). Remarkably, a recent study showed increased smoking abstinence after several sessions of ABM in a subsample of heavy smokers (Elfeddali et al., 2016). These mixed findings encourage the use of concomitant strategies to increase the effects of ABM.

Besides ABM strategies, transcranial electric stimulation (tES) has also been put forward as a promising option for modulating AB. tES refers to noninvasive brain stimulation methods that allow modulation of brain activity and connectivity *in vivo* by applying a low intensity current to the scalp. The rationale for using tES is to modulate AB by targeting its underlying brain network. In this way, studies have showed that applying tES over the dorsolateral prefrontal cortex (DLPFC), a brain region known to be involved in AB (Browning et al., 2010; Kang et al., 2012), can modulate AB in healthy individuals (Chen et al., 2017; Sagliano et al., 2017) and clinical populations such as social anxiety disorder (Heeren et al., 2017). Moreover, combining tES with ABM has been reported to augment the effects of ABM in healthy individuals (Clarke et al., 2014) and highly anxious individuals (Heeren et al., 2015a). Here, we used transcranial alternating current stimulation (tACS), as a new option for adjunctive neuroenhancement. tACS consisted in applying alternating current oscillating at a specific frequency through the scalp in order to increase intrinsic cortical oscillations at the applied frequency and modulate behaviors that are linked to these oscillations. Given the important role of alpha oscillations in cognitive control and attention (Dockree et al., 2007; Sadaghiani and Kleinschmidt, 2016), as well as smoking behaviors (Rass et al., 2016), we hypothesized that tACS applied at alpha frequency (10 Hz) will enhance the effects of ABM on smoking-related processes including AB and craving.

In this preliminary study, we aimed to investigate whether alpha-tACS applied over the DLPFC might boost the effects of ABM on clinical and cognitive features of TUD. To do so, we used a double blind design to compare the effects of ABM combined with active alpha-tACS to ABM combined with sham alpha-tACS on AB towards smoking, craving, and decision-making processes. We hypothesized that combining ABM with active alpha-tACS will reduce the attention towards smoking-related stimuli, reduce craving and reduce impulsivity in decision making more strongly than the combination of ABM and sham tACS.

2. Material and methods

2.1. Ethics statement

The study was carried out in accordance to the Declaration of Helsinki and approved by the local Ethics Committee and was registered in ClinicalTrials.gov database (NCT02810574). All participants gave their written informed consent after a detailed description of the aims of the study and the procedure.

2.2. Participants

Participants were recruited via advertisements posted on bulletin boards and emails sent to Université Laval's mailing lists (see Fig. 1, flowchart of the study). A total of 183 volunteers contacted our laboratory following the recruitment advertisement. From them, 123 individuals completed the telephone interview, 31 subjects completed the in-person screening interview with a trained researcher (MM) to assess eligibility (e.g., inclusion and exclusion criteria, including the assessment of the DSM5 criteria for TUD), and finally, 22 subjects were randomized to receive the intervention. To be eligible, participants had to be aged between 20 and 60, meet DSM 5 criteria for TUD, smoke at least 15 cigarettes per day for at least 1 year, have a score $\geq$ 4 at the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991), express the wish to quit smoking (answer "yes" to the question "Do you want to quit smoking?", seriously consider stop smoking in the next 6 months and have made at least one attempt to quit smoking) and have a normal or corrected-to-normal vision. Exclusion criteria included the use of taking psychotropic medications, actual or history of a psychiatric disorder other than TUD, and any contraindications to receive tACS (e.g., presence of metal in the head, history of serious brain injury, seizure, stroke or neurological diseases, severe or frequent headache, pregnancy). A total of 22 participants were enrolled in our study. Demographic information of the participants is presented in Table 1.

2.3. Design of the study

The study was designed as a double-blind, sham-controlled, cross-over experiment with two arms: 1) active tACS combined with ABM (tACS + ABM) and 2) sham tACS + ABM, delivered in a randomized order during two separated 2 -h visits at the laboratory. The two visits took place at the same time of the day and were separated by at least one week. At each visit, participants completed, in the same order, the Delay Discounting Task (DDT), a passive observation task with an eye tracking device to assess AB of smoking related stimuli, a smoking craving assessment with the Questionnaire of Smoking Urges, and a visual-probe task to assess AB of smoking related stimuli. These were administered before and after the (active, sham) tACS + ABM paradigm. Side effects and blinding were also assessed with standardized questionnaires. At the end of each visit, participants received compensation (20$) for their participation. Neither the participant, nor the experimenter was aware of the assigned tACS condition. Blinding was assessed with a standardized questionnaire in participants and outcome assessor. EEG was also recorded and results will be reported elsewhere.

2.4. Measures and tasks

Participants were tested individually in a dark quiet room. They were seated in front of a 21-inch computer screen, approximately 60 cm away from the center of the screen, in a height-adjustable chair, their chin on a chin rest. Both the chair and chin rest were adjusted and fixed to support head and limited movements during eye-movements recordings. All tasks and questionnaires were programmed using Matlab.

2.4.1. Delay Discounting Task

The DDT consists in inviting participants to make decisions between smaller, immediate rewards or larger, delayed rewards, thus assessing their cognitive impulsivity (Kirby et al., 1999). We used a DDT version composed of 112 trials that lasted approximately 6 min. In each trial, the amount of delayed reward was decided based on the hyperbolic function of delay discount, $V = A/(1+kD)$, where V is the value of the delayed outcome, A is the delayed reward, D in the length of the delay, and k is the steepness of the discount function. The 112 trials were composed of two different trials for each combination between eight fixed k values (0.0028, 0.005, 0.0275, 0.05, 0.075, 0.1, 0.3 and 0.5) and 6 fixed delays (1 week, 2 weeks, 1 month, 3 months, 6 months and 1 year). Participants were invited to make preferential choices by pressing either the left of right arrows on the keyboard with their dominant hand. Four different lists were used in order to vary between each time point (pre- and post-tACS + ABM) and each visit. The order of lists was randomized across participants. For each participant, each time point and each condition, we calculated the proportion of choices

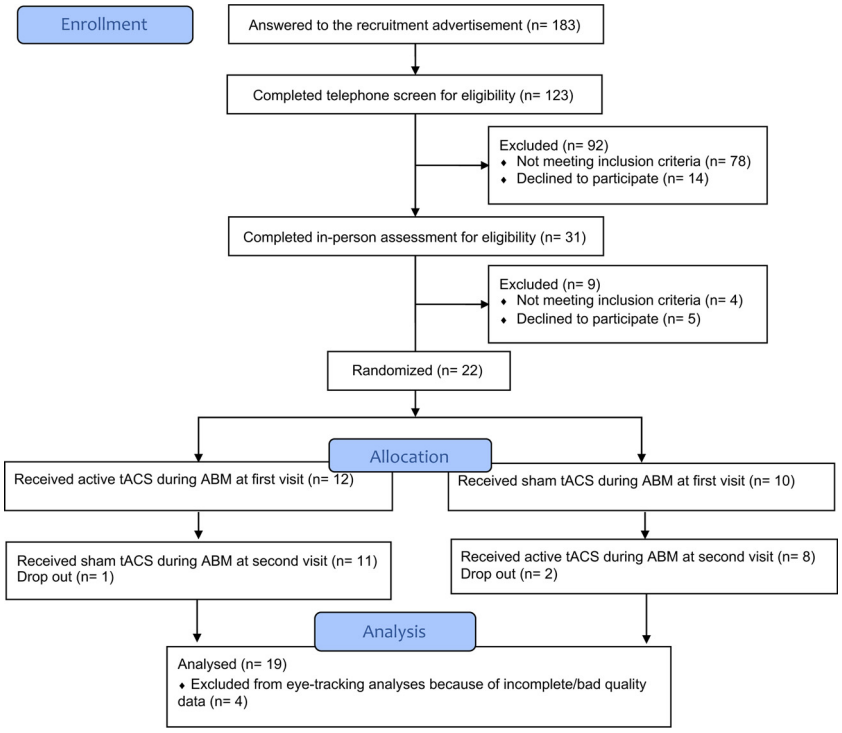

Fig. 1. Flowchart depicting passage of participants through the study.

Table 1
Demographic and clinical measures of the participants.

	Mean (N = 19)	SD
Sex (F/M)	5/14	
Age (years)	41.8	12.6
Education level (years)	13.5	2.5
Smoking duration (years)	23.6	11.3
FTND score (dependence level)	5.7	1.5
N cigarettes / day	19.8	4.3
BIS score (impulsivity)	61.5	9.7
Edinburgh Handedness Inventory score*	81.6	25.5

FTND: Fagerström Test for Nicotine Dependence; BIS: Barratt Impulsiveness Scale (Patton et al., 1995), *Oldfield, 1971.

in which the smaller and immediate reward was selected (Benningfield et al., 2014; Hamilton et al., 2015).

2.4.2. Passive observation of smoking related and neutral stimuli with eye-tracking

Participants completed a 2-min passive observation task during which their eye movements were recorded with an eye tracking device as a measure of AB. The task included 4 lists of 16 trials. Each trial included a group of 4 images. Different lists were used for pre- and post-tACS + ABM assessments at each visit. The order of lists was randomized across participants. Also, the 16 trials appeared in a different random order for each list and each participant. Each trial began with a central fixation cross presented at the center of the screen for a time that varies between 1750 and 2250 ms. Then, 4 images were simultaneously presented for 5000 ms, one in each different quadrant of the screen. The four-image group consisted of one smoking-related picture and three neutral pictures (one animal, one object, and one landscape). The position of the smoking-related picture varied across the trials with no more than two consecutive trials at the same position. Participants were asked to passively observe the images. Their eye fixations and movements were recorded using an eye-tracking device (ViewPoint Eye-tracker, Arrington Research). The proportion of time spent on the smoking-related quadrant was measured. Data with insufficient quality and/or trials where participants had not fixated on the fixation cross were excluded. Participants with less than 50 % of trials analyzable were excluded. This resulted in the exclusion of 4 participants.

2.4.3. Smoking craving assessment with the Questionnaire of Smoking Urges (QSU)

Craving was assessed using a computerized French version of the 12-item version of the QSU (Tiffany and Drobes, 1991). Each item was scored on a visual analogue scale ranging from "strongly disagree" to "strongly agree", calculated from 0 to 100 points. This questionnaire consists of four different subscales: desire to smoke, anticipation of positive outcome, relief from negative affect, and intention to smoke.

2.4.4. Attentional bias during visual-probe task with smoking related and neutral stimuli

Variants of the visual-probe task were used to assess the AB for smoking cues and to train attention via ABM (Fig. 2). The visual-probe task used to measure AB consisted of 120 trials. Each trial began with a central fixation cross presented for a time that varies between 500 and 750 ms. Participants were instructed to fix the cross at the start of each trial. Immediately after the cross presentation, two pictures, one neutral and one smoking-related, appeared concurrently on the screen for 500 ms, one on the left and one on the right side of the screen. Then, a probe appeared randomly and with equal frequency in place of the neutral or smoking-related image and remained on the screen until the participant gave a response. The probe was either an up arrow or a down arrow and participants were instructed to indicate whether the arrow was pointing up or down by pressing as quickly and accurately as possible the corresponding button (arrow) on the computer keyboard using their dominant hand. We used an equal number of trials in each condition as a function of the smoking-related picture location (left or right) and probe location (left or right). Stimuli were selected from the International Smoking Image Series (Gilbert and Rabinovich, 1999), the International affective picture system (Lang et al., 2008) and a personal collection. Stimuli consisted of 60 different pairs, each pair displaying neutral (e.g., pencil, person holding a stapler) and smoking-related images (e.g., cigarette, person lighting a cigarette), matched for sex,

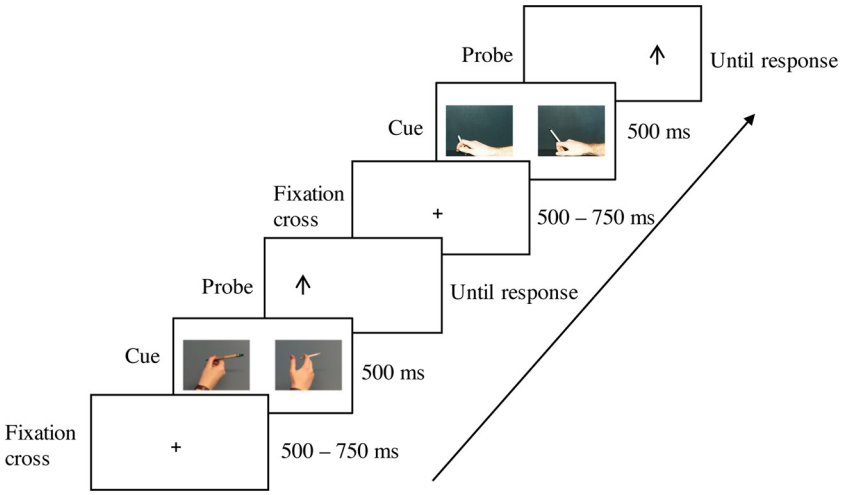

Fig. 2. Illustration of the visual-probe task used to train attention during the attentional bias modification (ABM) paradigm and to assess the attentional bias for smoking cues before and after the intervention. In the version of the task used for ABM, the probe always appeared in the same location of the neutral image. In the version of the task used to measure AB, the probe appeared in randomly and with equal frequency in the location of the neutral or smoking-related image.

age, and laterality (e.g. cigarette in left or right hand).

Half of the pairs (n = 30) were used for pre-tACS + ABM assessment and ABM paradigm, the other half were introduced in the post-tACS + ABM assessment as new images. For the pre-tACS + ABM assessment, each pair appeared four times in a randomized order. For the post-tACS + ABM assessment, the 30 trained pairs and the 30 new pairs appeared two times each. Each of the 120 trials appeared in a different random order for each participant and visit. Trials with incorrect responses or reaction times that were faster than 200 ms, slower than 2000 ms or 2 standard deviations greater or lower than each individual's mean reaction time within a condition type were excluded from the analyses. The AB was computed as the mean reaction time for trials in which the probe replaces the neutral stimulus *minus* the mean reaction time for trials in which the probe replaces the smoking-related stimulus. Positive AB scores indicates AB towards smoking-related stimuli and negative score represents AB towards neutral cues. For the post-tACS + ABM assessment, two AB scores were calculated: one for trained pictures and one for new pictures.

2.5. Interventions

2.5.1. Attention bias modification

The ABM paradigm started 5 min after the beginning of stimulation (active or sham). It consisted in a modified version of the visual-probe task used to measure AB in which the probe always appeared in the same location of the neutral image. The ABM consisted of 5 runs of 120 trials (600 trials). Participants were allowed to rest briefly after each run.

2.5.2. Transcranial alternating current stimulation

Transcranial alternating current was delivered using a battery-driven stimulator (Neuroconn DC-STIMULATOR Plus, Germany) with two 3 × 3 cm rubber electrodes positioned on the scalp at locations F4 and F3 (right and left DLPFC), according to the international 10/20 system for EEG. Electrodes were kept in place with adhesive, conductive ten20 paste (Weaver and Company, Aurora, CO, USA). tACS was delivered at 10 Hz (sinus mode) with a peak-to-peak intensity of 2 mA (0 μA offset). Duration of stimulation was 30 min for active tACS (18,000 cycles at 10 Hz) with a ramp up and ramp down period of 10 s (100 cycles). Sham tACS was performed with the same electrode montage as for the active tACS, but the current was delivered only during the first 60 s of the 30-min period. This approach mimics the typical sensations observed with active tACS under the electrodes at the beginning of stimulation. For blinding, the double blind study mode of the DC-stimulator was used so participants, tACS operators (CL, AC), and the outcome assessor (MM) were not aware of the stimulation condition. The study mode requires the tACS operators to enter a 5-digit code, different at each session, into the device, which corresponds to active or sham stimulation. The codes were selected among the device database and provided by an independent experimenter. Blinding was assessed in participants and the outcome assessor at the end of each visit with a visual analogue scale ranging from "I think that I have received sham stimulation" / "I think that the participant received sham stimulation" to "I think that I have received active stimulation", / I think that the participant received active stimulation", calculated from 0 to 100 points. tACS-related safety was assessed at each visit with a French translated version of a standardized questionnaire commonly used in tES experiments (Brunoni et al., 2011). More precisely, all participants completed a questionnaire that assesses 11 potential tACS-related side effects: headache, burning, itching, tingling, sensation of warmth, metallic taste, visual percepts (flash/phosphenes), cognitive changes, trouble concentrating, and acute mood changes. The intensity of these side effects was rated on a 4-points rating scale (1 = absent, 2 = mild, 3 = moderate, and 4 = severe).

2.6. Data analyses

Data were analyzed using the R-package for nonparametric ANOVA-type statistics analysis (nparLD function, R version 3.4.3 2017 The R Foundation for Statistical Computing) (Noguchi et al., 2012). This nonparametric rank-based model is robust to outliers. It allows analyzing data from small sample size and non-normally distributed data. Effects on AB scores for trained and for new images, percent of fixations on smoking pictures, craving, percent of immediate choices at the DDT, as well as side effects were separately analyzed using non-parametric ANOVA-type tests with stimulation condition (two levels: active, sham) and time (two levels: pre, post) as repeated measure factors (ld-F2 models). In case of significant interactions between condition and time factors, post-hoc tests were conducted also using nparLD (ld-F1 models). For graphical representations of the results, relative treatment effects (RTEs) estimated by the model were used with the corresponding 95 % confidence intervals (CIs). Blinding ratings were attributed to 3 categorical responses (0 – 33: sham; 33 – 66: unsure, 66 – 100: active) and compared between conditions using Fisher's exact test. All tests were two-tailed and statistical significance was set at $p < 0.05$.

3. Results

Summary statistics (mean, standard deviations (SD), RTE and 95 % CI) of all results are displayed in Table 2.

Table 2
Summary statistics of the results.

	Active tACS + ABM		Sham tACS + ABM	
	Pre	Post	Pre	Post
A) Effects on impulsive choices at the Delay Discounting Task (n = 19)				
% of choices of immediate rewards				
Mean (SD)	26.08 (16.63)	24.30 (20.61)	26.04 (21.71)	26.08 (21.07)
RTE (95	0.54	0.48	0.49	0.49
%CI)	(0.49 – 0.59)	(0.44 – 0.52)	(0.45 – 0.53)	(0.46 – 0.53)
B) Effects on attentional bias during passive observation of smoking related and neutral stimuli with eye-tracking (n = 15)				
% of time spent looking at the smoking-related quadrant				
Mean (SD)	28.90 (14.46)	20.90 (9.50)	25.20 (15.16)	24.79 (14.43)
RTE (95	0.59	0.42	0.51	0.48
%CI)	(0.53 – 0.65)	(0.33 – 0.52)	(0.45 – 0.57)	(0.41 – 0.55)
C) Effects on attentional bias at the visual-probe task with smoking related and neutral stimuli (n = 19)				
Attentional bias scores for trained images				
Mean (SD)	0.0064 (0.015)	−0.003 (0.027)	0.0073 (0.030)	−0.016 (0.035)
RTE (95	0.61	0.47	0.54	0.38
%CI)	(0.50 – 0.70)	(0.36 – 0.58)	(0.44 – 0.64)	(0.29 – 0.50)
Attentional bias scores for new images				
Mean (SD)	–	0.016 (0.040)	–	−0.00017 (0.022)
RTE (95	0.53	0.56	0.47	0.44
%CI)	(0.43 – 0.62)	(0.43 – 0.67)	(0.38 – 0.57)	(0.32 – 0.57)
D) Effects on smoking craving at the Questionnaire of Smoking Urges (n = 19)				
Ratings on the Desire to smoke subscale (range 0 – 300)				
Mean (SD)	112.00 (64.22)	99.53 (65.16)	96.89 (57.61)	119.42 (63.39)
RTE (95	0.51	0.48	0.46	0.56
%CI)	(0.46 – 0.55)	(0.42 – 0.53)	(0.40 – 0.53)	(0.51 – 0.60)
Ratings on the Anticipation of positive outcomes subscale (range 0 – 400)				
Mean (SD)	168.95 (96.51)	157.26 (86.13)	160.42 (89.24)	167.63 (83.13)
RTE (95	0.52	0.49	0.48	0.51
%CI)	(0.46 – 0.57)	(0.44 – 0.53)	(0.42 – 0.54)	(0.46 – 0.57)
Ratings on the Relief from nicotine withdrawal subscale (range 0 – 200)				
Mean (SD)	42.16 (49.58)	33.26 (37.78)	40.16 (44.82)	38.32 (43.82)
RTE (95	0.52	0.48	0.51	0.50
%CI)	(0.47 – 0.56)	(0.43 – 0.53)	(0.44 – 0.58)	(0.47 – 0.52)
Ratings on the Intention to smoke subscale (range 0 – 300)				
Mean (SD)	119.95 (67.63)	116.37 (57.11)	122.74 (59.45)	120.42 (56.27)
RTE (95	0.49	0.49	0.51	0.51
%CI)	(0.44 – 0.55)	(0.42 – 0.56)	(0.44 – 0.58)	(0.47 – 0.55)

AB: attentional bias (mean reaction time for trials in which the probe replaces the neutral stimulus *minus* the mean reaction time for trials in which the probe replace the smoking-related stimulus); ABM: Attention Bias Modification; RTE: relative treatment effects; SD: standard deviation; tACS: transcranial alternating current stimulation.

3.1. Effects on impulsive choices at the Delay Discounting Task (n = 19)

Results on percent of immediate choices revealed no significant main effects of Time (F_{ATS} = 2.36; p = 0.12) or Stimulation (F_{ATS} = 0.50; p = 0.48), but there was a significant Time x Stimulation interaction (F_{ATS} = 3.87, p = 0.049). Post-hoc tests revealed that the percent of immediate choices was significantly reduced with active tACS + ABM (p = 0.035), but not with sham tACS + ABM (p = 0.70), see Table 2A.

3.2. Effects on passive observation of smoking related and neutral stimuli with eye-tracking (n = 15)

The ANOVA-type statistics analysis on the percent of time spent on the smoking-related quadrant revealed a main effect of Time (F_{ATS} = 4.38, p = 0.04), no significant effect of Stimulation (F_{ATS} = 0.07, p = 0.79), but a significant Time and Stimulation interaction (F_{ATS} = 4.92; p = 0.03). Post-hoc tests revealed that the percent of time spent on the smoking-related quadrant was significantly reduced after active tACS + ABM (p = 0.01), but not after sham tACS + ABM (p = 0.32), see Table 2B.

3.3. Effects on smoking craving at the Questionnaire of Smoking Urges (n = 19)

The ANOVA-type statistics analysis revealed no significant main effects of Time (F_{ATS} = 1.05; p = 0.30) or Stimulation (F_{ATS} = 0.38; p = 0.54), but a significant Time and Stimulation interaction for the desire to smoke factor (F_{ATS} = 4.93; p = 0.026). Post-hoc tests indicated that the desire to smoke significantly increased after sham tACS + ABM (p = 0.030), but not after active tACS + ABM (p = 0.45). No significant interactions were found for the other components of craving: anticipation of positive outcome (F_{ATS} = 0.89; p = 0.35), relief from negative affect (F_{ATS} = 0.27; p = 0.60), and intention to smoke (F_{ATS} = 0.0001; p = 0.99). Results are displayed in Table 2C and Fig. 3.

3.4. Effects on attentional bias at the visual-probe task (n = 19)

To examine whether participants displayed an AB at pre-assessment, we compared reaction times to probes replacing smoking-related pictures to reaction times to probes replacing neutral pictures for each stimulation condition using nparLD (ld-F1 model). Analyses showed no significant AB towards smoking-related cues as measured by reaction times before active tACS + ABM (F_{ATS} = 3.27; p = 0.07), nor before sham tACS + ABM (F_{ATS} = 0.51; p = 0.47).

Analyses of the effect of tACS + ABM on AB scores based on reaction times revealed a main effect of Time for trained images (F_{ATS} = 5.11; p = 0.024), but no effect of Stimulation (F_{ATS} = 1.77; p = 0.18) or Time and Stimulation interaction (F_{ATS} = 0.021; p = 0.88). For new images, there were no significant effects of Time (F_{ATS} = 0.00019; p = 0.99), Stimulation (F_{ATS} = 1.57; p = 0.21) or Time and Stimulation interaction (F_{ATS} = 0.11; p = 0.74), see Table 2D.

3.5. Safety and blinding of tACS (n = 19)

tACS was well-tolerated by all participants and no differences were reported in side effects between active and sham tACS (all p < 0.05). Blinding ratings are displayed in Table 3. Analysis revealed a significant difference between tACS conditions regarding blinding ratings from participants (p = 0.02). They were able to correctly guess the stimulation condition 63 % of cases (23 sessions over 36). When blinding ratings at the first visit and at the second visit were considered separately, results showed significant differences between conditions at the second visit only (p = 0.01) and no significant differences in guessing at the first visit (p = 0.72). Analysis of blinding ratings of the outcome assessor also showed a significant difference between tACS conditions (p < 0.001). The experimenter was able to correctly guess the stimulation condition half of cases (19 sessions over 38). Results showed significant differences between conditions at the first (p = 0.04) and the second visit (p = 0.001).

4. Discussion

The present preliminary study explored the effects of alpha-tACS combined with ABM on clinical and cognitive features of TUD, specifically on the AB towards smoking cues, smoking craving, and decision-making. The main findings indicate that ABM combined with active alpha-tACS reduced the amount of time spent looking at smoking-related pictures during a passive viewing task using an eye tracking system, prevented the increase of the desire to smoke, and reduced impulsive choices at the DDT. While some studies previously reported beneficial effects of combining transcranial direct current stimulation applied over the DLPFC with ABM (Clarke et al., 2014; Heeren et al., 2015a), this seems to be the first study that used tACS in combination with ABM to target clinical and cognitive features of TUD such as smoking craving, attention to drug cues and decision-making. Since eye movement data are believed to provide an ecological and directly observable measure of the AB (Christiansen et al., 2015a; Field et al.,

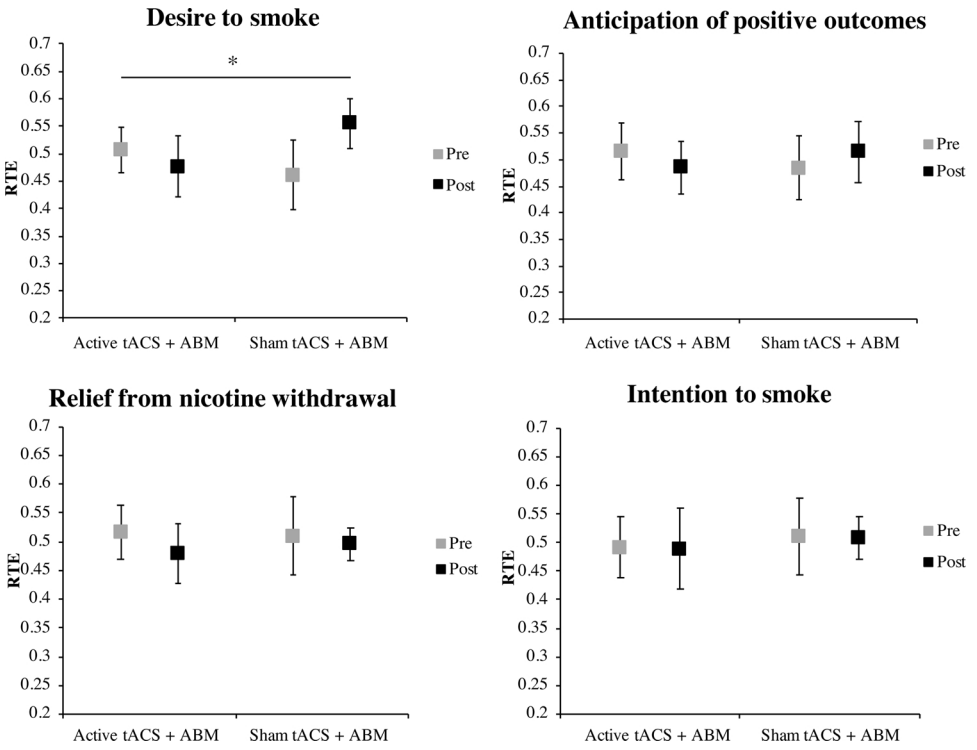

Fig. 3. Relative treatment effects (RTE) for the four subscales of the Questionnaire of Smoking Urge: desire to smoke, anticipation of positive outcome, relief from negative affect, and intention to smoke, before and after active tACS combined with ABM and sham tACS combined with ABM. Error bars represent confidence intervals of the RTE (N = 19).

Table 3
Distribution of blinding ratings among participants (n = 19) for each session.

Blinding ratings considering all tACS sessions			
	Guessed condition		
Correct condition	Active	Sham	Unsure
Active	12	4	3
Sham	4	11	4
Blinding ratings after the 1st tACS session			
	Guessed condition		
Correct condition	Active	Sham	Unsure
Active	5	3	3
Sham	2	3	3
Blinding ratings after the 2nd tACS session			
	Guessed condition		
Correct condition	Active	Sham	Unsure
Active	7	1	0
Sham	2	8	1

2004), the significant decrease of the amount of time spent fixating smoking-related pictures may reflect reduced allocation of attentional resources on motivationally salient cues after active alpha-tACS combined with ABM. Some authors explained the effect on dwell time on smoking cues by an increase in attentional control driven by the recruitment of the DLPFC (Heeren et al., 2015b, 2013). However, the effect was not observed on AB scores based on reaction times at the visual-probe task, neither for the images that were trained during ABM nor for new images. As proposed by Mogg et al. (2005) and Lochbuehler et al. (2018), one possible explanation for the inconsistent finding might be that the visual-probe reaction time assesses the focus of attention at a single time point during the trial, while eye movement recordings assess attention during the entire length of stimuli presentation. In addition, visual-probe AB scores have been reported to have low reliability (Chapman et al., 2019) in contrast to the proportion of viewing time (*i.e.* the time spent viewing the cue stimuli relative to neutral stimuli), which showed good reliability when assessed over 5 s (Waechter et al., 2014). Another explanation may be that the intervention did not induce significant changes at the visual-probe task because participants did not display any significant AB at baseline. This hypothesis is supported by Heeren et al.'s study, which pointed out larger reductions in AB scores following ABM in participants who had greater AB at baseline (Heeren et al., 2015b). However, some studies in substance-use disorder found that ABM was able to significantly diminish attention to substance-related cues even when no significant AB was reported at baseline (Field and Eastwood, 2005; Field et al., 2007; Schoenmakers et al., 2007, 2010; for a review see Heitmann et al., 2018).

The current study also reported that active alpha-tACS combined with ABM prevented the increase of the self-reported desire to smoke at the QSU that was observed with sham alpha-tACS combined with ABM. Similar effect on the desire to smoke dimension was also previously reported with transcranial direct current stimulation applied over the DLPFC (Fecteau et al., 2014). The combination of active tACS and ABM had no effect on the other subdimensions of craving, namely the anticipation of positive outcome from smoking, the relief from negative affect and the intention to smoke.

The combination of active alpha-tACS and ABM also reduced the proportion of immediate choices at the DDT. These results suggest that active alpha-tACS combined with ABM can reduce impulsive decision-making. Some previous studies reported a reduction of impulsive decision-making using other noninvasive brain stimulation techniques applied over the DLPFC. For instance, Cho et al. (2010) reported that continuous theta burst stimulation over the right DLPFC reduced the steepness of the discount function at the DDT in healthy subjects. Kekic et al. (2017) reported that tDCS with the anode over the right and cathode over the left DLPFC, or with the reverse electrode montage, may decrease the tendency to choose immediate rewards at a temporal discounting task in adults with bulimia nervosa. These findings support

the hypothesis of an effect of the intervention on motivational processes, particularly appetite for reward, including appetite for smoking but also for monetary rewards, as shown by DDT results. Still, one has to consider how a between-condition difference on a 2-choice hypothetical DDT may translate into real world contexts.

Taken together, these preliminary results support the hypothesis that tACS combined with ABM may reduce the incentive motivational properties of smoking-related cues. These cues may become less salient and attract less attention during free and passive observation of them. Ultimately, this may diminish the desire to smoke and impulse choices. It is important to mention that while the tACS electrodes were placed over the DLPFC, the alternating current flows between the two electrodes, thus it likely modulated several prefrontal areas implicated in substance use, such as the medial PFC and the anterior cingulate cortex. In addition, previous studies have reported that tACS may have widespread effects by modulating functional connectivity between directly targeted areas and more distant regions (Cabral-Calderin et al., 2016; Mondino et al., 2020).

This study has several limitations. First, findings indicated that blinding of the participants regarding tACS condition was not successful. Indeed, participants correctly identified the nature (active, sham) of the stimulation condition in approximately 63 % of cases. These results were observed independently of the occurrence of side-effects, such as itching and phosphenes, which did not significantly differ between tACS conditions. Since the study-mode of the tACS device was used, and since neither the experimenter nor the participants were informed of the condition, we believe that this blinding issue might be mostly related to the use of a crossover design. Indeed, separate analyses of the two visits showed that participants were able to guess their stimulation condition beyond chance only at the second visit. Similar findings of inadequate participants blinding have been reported in a crossover study applying transcranial direct current stimulation at a 2 mA intensity (O'Connell et al., 2012). The outcome assessor was able to correctly identify the nature of the stimulation condition in about half of the cases. Thus, blinding of the outcome assessor was not fully successful. The outcome assessor was mainly biased by the presence of artifacts on EEG signals that were recorded during tasks following tACS administration (data reported elsewhere). Of note, all tasks were programmed and administered by a computer with the instructions displayed on the screen (including the QSU questionnaire), thus the interaction between the outcome assessor and participants was kept to a minimum. Secondly, the study did not include a condition investigating the impact of alpha-tACS without ABM. As a consequence, the present results should be interpreted with caution. Since no differences were found between pre- and post-assessment in the sham tACS + ABM condition, we cannot rule out that the effects of active tACS + ABM on eye-movement data, craving and decision-making might result from the tACS alone and not the combination with ABM. Further studies should be conducted in order to disentangle the effects of tACS and ABM. Finally, the study included a single active tACS condition, delivered at alpha frequency over the DLPFC. This design did not allow us to investigate the specificity of the frequency or brain region tested. Future studies should include an active control condition by delivering tACS at another frequency and other brain regions to shed light on this issue.

5. Conclusion

In summary, this preliminary study suggests that combining alpha-tACS with ABM can have a significant effect on the attention towards smoking-cues as assessed by eye movement recordings, desire to smoke, and impulsivity in decision-making. As such, alpha-tACS combined with ABM may help smokers who wish to quit to reduce their craving and desire to smoke by reducing covert processes involved in the motivation to smoke, such as attention towards smoking-cues, and associated cognitive features, such as impulsive decision-making. Further studies are needed to investigate how these effects might translate to smoking behaviors such as cigarette consumption.

Contributors

MM and SF conceived and designed the study. ER helped with implementing the experimental tasks. MM, CL and AC ran the experiment. MM analyzed the data, interpreted the findings, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Role of the funding source

Nothing declared.

Declaration of Competing Interest

No conflict declared.

Acknowledgments

This study was financially supported by a Canada Institutes of Health Research grant to SF. MM was supported by a postdoctoral fellowship from Canada Institutes of Health Research. SF was supported by the Canada Research Chair in Cognitive Neuroplasticity.

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