Electrophysiological and Behavioral Effects of Combined Transcranial Direct Current Stimulation and Alcohol Approach Bias Retraining in Hazardous Drinkers

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Background: Cognitive bias modification (CBM) can be used to retrain automatic approach tendencies for alcohol. We investigated whether changing cortical excitability with transcranial direct current stimulation (tDCS) could enhance CBM effects in hazardous drinkers. We also studied the underlying mechanisms by including behavioral (craving, implicit associations, approach tendencies) and electrophysiological (event-related potentials) measurements.

Methods: The analytical sample consisted of 78 hazardous drinkers (Alcohol Use Disorders Identification Test >8) randomly assigned to 4 conditions in a 2-by-2 factorial design (control/active CBM and sham/active tDCS). The intervention consisted of 3 sessions of CBM, specifically alcohol approach bias retraining, combined with 15 minutes 1 mA tDCS over the left dorsolateral prefrontal cortex. There was a pre- and postassessment before and after the intervention that included experimental tasks (Approach Avoidance Task, Implicit Association Task) and an electroencephalogram with an oddball and cue-reactivity task.

Results: tDCS decreased cue-induced craving (but not overall craving) on postassessment. CBM did not induce an avoidance bias during assessment. During the training, active and control-CBM only differed in bias score during the first session. We found no enhancement effects of tDCS on CBM. Electrophysiological data showed no clear effects of active tDCS or CBM on the P300.

Conclusions: There were no electrophysiological or behavioral effects of repeated CBM and/or tDCS, except for an effect of tDCS on craving. Applied in these specific ways these techniques appear to have limited effects in a hazardous drinking population.

Key Words: tDCS, CBM, EEG, Alcohol, Hazardous Drinkers.

YOUNG ADULTS, ESPECIALLY college students, show excessive and hazardous drinking (Hingson et al., 2009). In hazardous drinkers, a relation has been found between implicit alcohol biases and alcohol consumption or alcohol-related problems (Wiers et al., 2007). Implicit alcohol biases represent preferences in processing of alcohol-related information and can be measured with for example, an Implicit Association Test (IAT; Palfai and Ostafin, 2003), a Visual Probe Task (Townshend and Duka, 2001), or an Approach Avoidance Test (AAT; Wiers et al., 2009). In a cognitive bias modification (CBM) paradigm, some of these tasks are adapted into a training version (review: Wiers et al., 2013). In a specific type of CBM, the alcohol approach bias retraining, people learn to avoid alcohol stimuli by pushing them with a joystick. A single session of this training was found to reduce the alcohol approach bias in hazardous drinkers and in those successfully trained (i.e., became faster to avoid alcohol) reduced alcohol consumption in a subsequent taste test (Wiers et al., 2010). In 2 patient studies, the training was effective in reducing relapse (Eberl et al., 2013; Wiers et al., 2011), and these outcomes were mediated by changes in alcohol approach action tendency and approach association (Eberl et al., 2013; Gladwin et al., 2015). We are interested in further enhancing bias changing effects of retraining with transcranial direct current stimulation (tDCS).

tDCS is a neuromodulation technique with which a small electrical current is sent through the brain, believed to influence excitability (Nitsche and Paulus, 2000). Changes in neural excitability and plasticity arise via cellular mechanisms that can influence membrane polarization (Monai et al., 2016; Nitsche et al., 2003). Due to changes in neuronal processes, electrical currents can increase cortical blood flow (a measure of brain activity) and modulate cortical connectivity (Stagg et al., 2013; Zheng et al., 2012); the exact neural effects are still under investigation, but the effects are likely variable and task dependent. By modulating the cortical activity and possibly increasing efficiency, tDCS can influence cognitive processes. Working memory performance,

which is highly dependent on the dorsolateral prefrontal cortex (DLPFC), has often been successfully improved with tDCS over the DLPFC (review: Brunoni and Vanderhasselt, 2014). By also affecting NMDA receptors (Monte-Silva et al., 2013; Nitsche et al., 2003), tDCS could enhance plasticity in the brain and is therefore of interest to the goal of enhancing learning effects of cognitive training (Elmasry et al., 2015) and in this study more specifically CBM. For example, greater attentional bias modification was obtained after a single session of DLPFC tDCS (Clarke et al., 2014). And better stop signal performance was found after a behavioral inhibition training combined with anodal right inferior frontal gyrus (rIFG; an area involved in inhibitory processes) stimulation compared to sham stimulation (Ditye et al., 2012). In a sample of heavy drinkers, rIFG stimulation did not reduce craving, whereas left DLPFC stimulation did (den Uyl et al., 2015); others also show the potential clinical relevance of DLPFC stimulation for alcohol craving (Boggio et al., 2008). Changing DLPFC activity is relevant in relation to implicit biases, since when cognitive control (of which working memory is a component of) is low, people are driven more by implicit alcohol biases (Wiers et al., 2013). Also in cannabis users, higher DLPFC activation during an approach trial predicted a decrease in problem severity (Cousijn et al., 2012).

In this study, we investigated whether tDCS could enhance the effects of alcohol approach bias retraining on alcohol-related implicit cognitive processes and drinking behavior. To further investigate the possible mechanisms of CBM and tDCS, we included a electrophysiological measurement with an electroencephalogram (EEG). Event-related potentials (ERPs) can signal abnormal processes that may contribute to the etiology of alcohol addiction. The P300, a positive peak appearing around 300 to 600 ms after presentation of an infrequent stimuli (Polich and Kok, 1995), is frequently studied and is believed to be able to signal motivational and emotional relevance (Hajcak et al., 2010). Previous research has shown that in an oddball task, with frequent nontarget stimuli and infrequent target stimuli, hazardous drinkers, and binge drinkers have a higher P300 peak for alcohol target stimuli (Ceballos et al., 2012; Petit et al., 2013). Also those hazardous drinkers with a higher risk for dependence showed increased P300 for alcohol stimuli (Bartholow et al., 2007, 2010), and alcohol-dependent patients with increased P300 for alcohol were more likely to relapse (Petit et al., 2015). This P300 response can be useful to measure the objective motivational salience alcohol stimuli have.

In this study, we use behavioral and electrophysiological measures to investigate whether tDCS can enhance CBM in hazardous drinkers. The participants received 3 sessions of a combination of (sham/active) tDCS and (control/active) CBM. Before and after these training sessions, they performed 2 implicit tasks to measure their alcohol approach bias, and they completed an oddball task and cue-exposure task, during which EEG was measured. We expected that tDCS facilitated CBM would improve scores on alcohol-related measures (such as reduced craving, bias, etc.). The factorial design also makes it possible to compare main effects of tDCS and CBM on behavioral and electrophysiological measures to further explore the underlying mechanisms of these techniques.

MATERIALS AND METHODS

Participants

The recruitment message for this study aimed at finding participants who drank heavily and would like to cut back on their drinking. Participants were selected for participation if they scored higher than 8 on the Alcohol Use Disorders Identification Test (AUDIT) (indicating hazardous drinking; Saunders et al., 1993), but no screening questionnaire was used for motivation. Participants were screened for tDCS safety criteria (for an overview such as epilepsy, neurological damage, see e.g., den Uyl et al., 2015). We included 86 participants in the study, of which 6 dropped out during the experiment (scheduling difficulties) and 2 participants were excluded (1 was a heavy cannabis user; 1 did not speak fluent Dutch). The analytical sample resulted in 78 Dutch-speaking participants (51 women, 27 men) between the age of 18 and 35 (mean: 21.8, SD: 3.2). All participants were randomly assigned to 1 of the 4 conditions of the 2-by-2 factorial design. All participants gave written informed consent, and the study was approved by the local ethical committee. Participants received either 60 euros or participation credits for completing the experiment.

Intervention

Transcranial Direct Current Stimulation. The stimulation was administered with two 35-cm^2 electrodes inserted in saline-soaked sponges. With rubber straps, the anodal electrode was placed on the F3 position of the 10 to 20 EEG system (corresponding to the DLPFC area) and the cathodal above the contralateral supraorbital region. For active stimulation, the current was held constant at 1 mA for 15 minutes, which is a current strength commonly and successfully used in studies with healthy participants (e.g., Clarke et al., 2014; Gladwin et al., 2012; den Uyl et al., 2015). For sham stimulation, the device was automatically turned off after 30 seconds. The DC-stimulator plus device (neuroConn GmbH, Ilmenau, Germany) has a blinding function, so that neither participant nor experimenter was aware of whether active or sham stimulation was administered. The participants received only 1 session of (sham/active) tDCS a day and received 3 sessions within 3 or 4 days.

Approach Bias Retraining. While receiving the stimulation, participants performed the approach bias retraining. In this training, participants viewed alcohol and nonalcoholic pictures and responded to the orientation (here: left or right tilt; cf. Cousijn et al., 2011) of the pictures, which caused either alcohol or nonalcoholic pictures to be pulled or pushed (cf. Wiers et al., 2010). In the active training, 90% of the alcohol stimuli required a pushing movement with a joystick (during which the picture size also decreases, visualizing avoidance), and 10% of the alcohol pictures required a pulling movement (and vice versa for the nonalcohol pictures). In the control training, the contingency was kept at 50%, so remained in assessment phase (cf. Wiers et al., 2011, 2013). The stimuli set consisted of 25 alcohol and 25 nonalcohol pictures from the Amsterdam Beverage Picture Set (Pronk et al., 2015). The training consisted of 3 blocks of 100 trials. During training session, 2 and 3 participants received the whole training 1 more time after the tDCS was finished to maximize potential training effects.

Questionnaires

The AUDIT was used to screen for alcohol-related problems, where someone with a score of 8 or higher (of 40) is considered a hazardous drinker (Saunders et al., 1993). The Fagerström Test for Nicotine Dependence contained several questions assessing the severity of nicotine dependence (Heatherton et al. 1991). The items were summed to reach a score between 0 (very low dependence) and 10 (high dependence). The Readiness to Change Questionnaire (RCQ) contained 12 questions and measured different stages (contemplation, precontemplation, action) of motivation to change drinking behavior (Budd and Rollnick, 1996). A continuous scale (with precontemplation reverse scored) was used where positive scores represented higher motivation and negative scores lower motivation (range −24 to +24) (Forsberg et al., 2004). The Alcohol Approach and Avoidance Questionnaire measured craving (McEvoy et al. 2004). We used the inclined scale, measuring inclinations to approach alcohol, as an outcome measurement, because it contained mild craving questions (den Uyl et al., 2015).[1] This scale consisted of 4 questions on a 9-item Likert scale, where higher scores indicated higher craving. To measure alcohol use, participants filled out how much they had drunk on each day of the preceding week. A calendar and an explanation of a standard drink (10 mg alcohol) were given as assistance. All drinks in the preceding week were summed to obtain a total score. Side effects due to tDCS were measured after each stimulation session. On a 4-item scale, participants indicated whether they experienced itching, burning, tingling, pain, headache, nausea, dizziness, or fatigue.

Behavioral Outcome Measurements

Approach Avoidance Task. The AAT is the assessment form of the approach bias retraining. In this task, 50% of the alcohol pictures were presented in push format and 50% in pull format (same for nonalcoholic pictures). The task consisted of 96 trials. An approach bias was measured by calculating the median reaction time for each category and then subtracting the push and pull trials for both picture types and then subtracting the alcohol approach bias score from the nonalcohol approach bias score, so that a positive score indicated an approach bias toward alcohol (Wiers et al., 2009).

Implicit Association Test. The IAT is a classification task that measured the strength of association between 2 concepts (Greenwald et al., 1998). Participants were required to categorize words into 2 categories: alcohol versus nonalcohol, and approach versus avoidance (Ostafin and Palfai, 2006). These categories were shown on each side of the screen, while words (e.g., beer, cola, take, avoid) appear in the center of the screen that were categorized with a left (F) or right (J) button press. In an approach alcohol block, alcohol and approach words (and nonalcohol and avoidance) were categorized with the same response, and in an avoid alcohol block, alcohol and avoid words (and nonalcohol and approach) were categorized with the same response. For each category, 5 different target words were used. The 7-block structure was used, with single categories practice blocks (1, 2, 5), practice blocks (3, 6) with both categories (10 trials), and experimental blocks (4, 7) with both categories (40 trials). In block 5, the approach avoidance categories switch, so that 2 different blocks (alcohol approach vs. alcohol avoid) were created, and the order was counterbalanced across participants. An approach bias was determined by subtracting the average reaction time for the alcohol approach block from the alcohol–avoidance block; positive scores represented an approach association with alcohol.[2]

Electrophysiological Outcome Measurements

Alcohol Oddball Task. In the oddball task in each block, 48 frequent (office supplies) stimuli were shown and 16 infrequent (8 alcohol, 8 nonalcohol) stimuli were shown. Each block was repeated 4 times, resulting in 32 (12.5%) alcohol trials, and 32 (12.5%) nonalcohol trials. The participants were instructed to push the left button (left hand) for objects and the right button (right hand) for beverages (button press was counterbalanced). The stimuli were shown for 800 ms, and interstimulus interval was jittered between 1,000 and 1,400 ms.

Cue Craving Task. In the craving task, alcohol or nonalcohol pictures were presented on the screen for 800 ms, after which a green screen indicated that participants could give a response to the question how much they desired the drink they just viewed. Answers were given on a scale from 1 to 4 (not at all, a little, much, very much), with number 1 to 4 on the keyboard with the right hand. The order (1 = not at all, vs. very much) was changed in the middle of the task and practiced before each block so participants could indicate the right feeling without looking at the keyboard. Twenty-four alcohol pictures and 24 nonalcohol pictures (of different types, e.g., beer and wine) were shown twice (resulting in 48 trials). Interstimulus interval (after response) was jittered between 900 and 1,100 ms.

EEG Recording and Analysis. Electrophysiological data were recorded from 64 scalp electrodes with a Biosemi system (Amsterdam, the Netherlands). Six bipolar electrodes were used: 4 were placed around the eyes to measure the horizontal and vertical eye movements, and 2 were placed on the mastoids as a reference. Data were recorded with a sampling rate of 1,024 Hz. A low-pass filter of 100 Hz was used, and data were down sampled to 256 Hz offline. Data analysis was performed with Brain Vision Analyser Software (version 2, ; Brain products GmbH, Gilching, Germany). All electrodes were rereferenced to the mastoids. A high-pass filter of 0.01 was used, and an extra 30 Hz low-pass filter was used for ERP analysis. The algorithm of Gratton and colleagues (1983) was applied for ocular correction.

Epochs (−200, 800) around stimulus presentation were created and baseline corrected for both tasks. Epochs with artifacts were deleted using semiautomatic artifact rejection. In the oddball per subject, an average of 4.9 (pre-assessment) and 6.4 (postassessment) segments were deleted, and in the craving task, an average of 6.8 (pre-assessment) and 5.8 (postassessment) were deleted. There were no significant differences in amount of deleted segments between conditions ($p > 0.24$), or beverage stimuli types ($p > 0.16$). Epochs were averaged for each stimuli category. Peak detection was used to find the P3; for the oddball task, the peak between 300 and 650 ms after stimulus presentation was used, and as the ERP of the craving task showed 2 peaks, P3 was determined between 300 and 450 ms, and P3 extended (P3e) between 450 and 700 ms. The maximum amplitude were extracted for each stimulus type (alcohol vs. nonalcohol). We analyzed the peaks on the frontal and parietal right, central, and left, electrodes (F5, Fz, F6, P5, Pz, P6).

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[1]We also included a short 6-item Desires for Alcohol Questionnaire before and after tDCS, which showed floor effects (only asks for strong feelings of craving) and thus was not included.

[2]We also administered an IAT with valence words; however, this is not included in this study, since hazardous drinkers generally have a negative bias (den Uyl et al., 2015). We also administered a paper-and-pencil Stroop, which is also not included.

Procedure

Participants were screened for eligibility via email. Participants filled out the baseline questionnaires (AUDIT, Situational Confidence Questionnaire, RCQ, demographic questions) online (3 to 0 days) before the experiment. The participants performed the following questionnaires and tasks (in this order): alcohol use, craving, AAT, IAT, EEG (craving, oddball task), once in the pre-assessment and once in the postassessment.[3] In addition to this, participants performed a craving questionnaire and another AAT assessment task before the second and the third intervention session. The first intervention session was administered immediately after the pre-assessment. All sessions were completed in the afternoon within 5 (mostly week) days. One week and 1 month after the experiment, participants received an email with follow-up questionnaires (alcohol use, RCQ).

Statistical Analysis

All outcome measurements were analyzed with a repeated-measures analysis of variance (ANOVA) with time (2, 3, or 4 measurements) as within factor, and the condition CBM (control vs. active) and tDCS (sham vs. active) as between-subject variables. Some specific analyses included the within-factor stimulus type (alcohol vs. nonalcohol). For the ERP analysis, we also included the specific electrodes as within-factors location (parietal vs. frontal) and hemisphere (left, central, and right).

RESULTS

There were no significant differences on baseline measurements between conditions (Table 1). Most participants tolerated the stimulation well. When each side effect was averaged over all sessions, there was an interaction with tDCS and side effect type, $F(7, 518) = 9.67$, $p < 0.01$, $\eta_p^2 = 0.12$. Follow-up analysis for each side effect shows that after active tDCS ($M = 2.59$, SE = 0.15), participants report more itching then after sham ($M = 1.75$, SE = 0.11, $t(67) = -4.42$, $p < 0.01$); participants report less fatigue ($M = 1.78$, SE = 0.16) and slightly less nausea ($M = 1.02$, SE = 0.02) after active tDCS than after sham-tDCS (fatigue: $M = 2.41$, SE = 0.13, $t(67) = 3.07$, $p < 0.01$, nausea: $M = 1.1$, SE = 0.03, $t(67) = 2.22$, $p = 0.02$).

Behavioral Results

Approach Bias. The ANOVA showed no significant effect of time (over 4 sessions, although a statistical trend was observed, $p = 0.06$), and no significant interaction with tDCS or CBM ($p > 0.5$). There was, however, a significant main effect of CBM, $F(1, 72) = 5.85$, $p = 0.02$, $\eta_p^2 = 0.08$. Although at baseline (or any other single session), the difference between active and control-CBM is nonsignificant ($p = 0.12$), when all sessions were taken together participants in the CBM group had a stronger avoidance bias (Fig. 1).

To examine the possible tDCS effects more thoroughly, we also analyzed the approach bias during training. As in the training, the contingency was 90 to 10%, and it was possible to calculate an approach bias with the few available approach alcohol trials. The sessions during which participants received tDCS were included in the ANOVA. As to be expected, there was a main effect of CBM, $F(1, 74) = 5.10$, $p = 0.03$, $\eta_p^2 = 0.06$, and there was also an interaction with CBM and time, $F(2, 73) = 7.26$, $p < 0.01$, $\eta_p^2 = 0.17$. The interaction with time showed that there was a difference in bias during training session 1, $t(50.81) = 3.53$, $p < 0.01$, but that this difference disappeared in sessions 2 ($p = 0.21$) and 3 ($p = 0.14$, Fig. 1). Even though in 1 condition, alcohol approach trials only occur in 10% of the task, and there is no difference in reaction times for frequent and infrequent trials after 1 training session. There was no interaction with tDCS ($p > 0.7$).

Approach Association Bias. The ANOVA only showed a significant effect of time (pre- vs. postassessment, $F(1, 74) = 10.25$, $p < 0.01$, $\eta_p^2 = 0.12$), the approach bias went from slightly positive at pre-assessment ($M = 6.40$, SE = 16.03) to more negative at postassessment ($M = -38.50$, SE = 12.71). There was no interaction with tDCS or CBM ($p > 0.26$).

Craving Inclined Score. The ANOVA only showed a significant effect of time (session × 4, $F(3, 222) = 2.81$, $p = 0.04$, $\eta_p^2 = 0.04$); craving decreased over time, follow-up contrasts showed that compared to session 1 ($M = 5.07$, SE 0.18), there was a significant reduction at sessions 3 ($M = 4.48$, SE = 0.22, $F(1, 74) = 8.59$, $p < 0.01$, $\eta_p^2 = 0.10$), and 4 ($M = 4.56$, SE = 0.25, $F(1, 74) = 4.14$, $p = 0.046$, $\eta_p^2 = 0.05$), but not session 2 ($M = 4.77$, SE = -0.21, $p = 0.13$). There was no interaction with tDCS or CBM ($p > 0.18$).

Alcohol Use Previous Week. There was a trend for an effect of time (pre-assessment, 1-week follow-up, 1-month follow-up),[4] $F(2, 74) = 2.70$, $p = 0.071$, $\eta_p^2 = 0.35$); planned contrasts showed that from pre-assessment ($M = 21.02$, SE = 1.61) to 1-week follow-up ($M = 16.7$, SE = 1.5), there was a significant decrease of alcohol use in the previous week, $F(1, 74) = 5.05$, $p = 0.03$, and the decrease 1-month follow-up ($M = 17.25$, SE = 1.85) did not reach significance, $F(1, 74) = 3.44$, $p = 0.07$. There was no interaction with tDCS or CBM ($p > 0.61$).

Electrophysiological Results

Alcohol Oddball Task. Due to noise in the EEG recording, 7 participants were excluded from the analysis. Analysis of the reaction times of the oddball task with time and

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[3]Data not included in this article: During EEG measurement, participants first performed a 3-minute eyes-closed resting state. They also filled out short questions regarding their mood and sleep quality and gave a saliva sample for genetic analysis.

[4]Postassessment is not included because it overlaps partly with the pre-assessment.

Table 1. Demographic and Baseline Variables

Group	1. M	1. SE	2. M	2. SE	3. M	3. SE	4. M	4. SE	Total M	Total SE	p-Value
n	20		19		20		19		78		
F/M	13/7		12/7		14/6		12/7		51/27		0.97
Age	20.95	0.43	22.79	0.88	21.80	0.86	21.89	0.60	21.85	0.36	0.23
AUDIT	16.10	0.77	15.32	0.86	17.60	1.02	15.74	1.25	16.21	0.49	0.59
RCQ	0.63	0.45	0.63	0.38	0.50	0.40	0.54	0.41	3.57	0.20	0.97
% smokers	40.0		42.1		40.0		26.3		37.2	0.4	0.73
FTND	1.25	0.37	0.88	0.40	0.88	0.40	0.00	0.00	0.83	0.19	0.52
SCQ	5.28	0.37	5.42	0.39	5.11	0.45	6.39	0.38	5.91	0.28	0.16
Alcohol use previous week	23.76	3.88	17.79	2.88	23.22	2.59	19.32	3.40	21.08	1.61	0.75
Craving inclined scale	4.83	0.27	5.60	0.38	5.06	0.36	4.80	0.43	5.07	0.18	0.16
Approach bias	7.05	18.57	5.84	11.36	−10.78	18.29	−29.95	19.09	−6.83	8.60	0.60
Association bias	14.48	38.01	21.18	34.35	30.98	28.01	−44.34	24.26	6.02	15.90	0.28

AUDIT, Alcohol Use Disorders Identification Test; RCQ, Readiness to Change Questionnaire; FTND, Fagerström Test for Nicotine Dependence; SCQ, Situational Confidence Questionnaire.

stimulus type (alcohol vs. nonalcohol) showed a significant decrease over time, $F(1, 67) = 8.38$, $p < 0.01$, $\eta_p^2 = 0.11$. There was also a main effect of stimulus type, $F(1,$

Fig. 1. Approach bias data. (**A**) Shows the alcohol approach bias (reaction time difference score) at the beginning of each session. Those in the control-cognitive bias modification (CBM) condition have a larger approach bias overall. (**B**) Shows the alcohol approach bias for the training sessions; in the first training, participants have an avoidance bias in the active CBM condition (push alcohol), but this disappears in the second and third training. Error bars represent standard error of the mean.

$67) = 25.12$, $p < 0.01$, $\eta_p^2 = 0.27$, and participants responded faster to alcohol stimuli ($M = 484.53$, SE = 5.52), than nonalcohol stimuli ($M = 472.98$, SE = 5.61).

The ANOVA with P300 amplitude showed a main effect of time, $F(1, 67) = 13.30$, $p < 0.01$, $\eta_p^2 = 0.17$, due to a decrease in the overall P300 for targets. It also showed a main effect for location, $F(1, 67) = 343.73$, $p < 0.01$, $\eta_p^2 = 0.83$, and hemisphere, $F(2, 134) = 47.7$, $p < 0.01$, $\eta_p^2 = 0.46$, and also a significant interaction Location × Hemisphere, $F(2, 134) = 22.45$, $p < 0.01$, $\eta_p^2 = 0.25$, reflecting that the P300 was highest on Pz (Fig. 2). There was a significant interaction with stimulus type and location, $F(1, 67) = 8.86$, $p < 0.01$, $\eta_p^2 = 0.18$; the P300 for alcohol pictures was larger on the parietal electrodes, but not on the frontal electrodes. There were no significant interactions with time, stimulus type, and condition.

Cue Craving Task. Due to noise in the EEG recording, 8 participants were excluded. Analysis of the craving responses showed a significant main effect of time, $F(1, 65) = 5.36$, $p = 0.02$, $\eta_p^2 = 0.08$, and of stimulus type, $F(1, 65) = 195.23$, $p < 0.01$, $\eta_p^2 = 0.75$, which indicated that craving decreased the second session and was higher for nonalcohol pictures. There was also a significant interaction with time and tDCS, $F(1, 65) = 8.01$, $p < 0.01$, $\eta_p^2 = 0.11$, which showed that tDCS decreased craving. The interaction with stimulus type was not significant ($p = 0.56$). However, as we were specifically interested in alcohol craving, we analyzed the stimuli separately and there was an interaction with time and tDCS for alcohol pictures, $F(1, 65) = 4.43$, $p = 0.04$, $\eta_p^2 = 0.06$ (and no interaction for nonalcohol pictures; $p = 0.15$). This showed that tDCS reduced cue-evoked craving for alcohol, note, however, that there is already a trend level difference at baseline ($p = 0.10$) (Fig. 3).

The ANOVA for the P300 amplitude showed a main effect of location, $F(1, 65) = 368.44$, $p < 0.01$, $\eta_p^2 = 0.85$, and hemisphere, $F(2, 130) = 5.08$, $p < 0.01$, $\eta_p^2 = 0.07$, and a significant Location × Hemisphere interaction, $F(2, 130) = 27.79$,

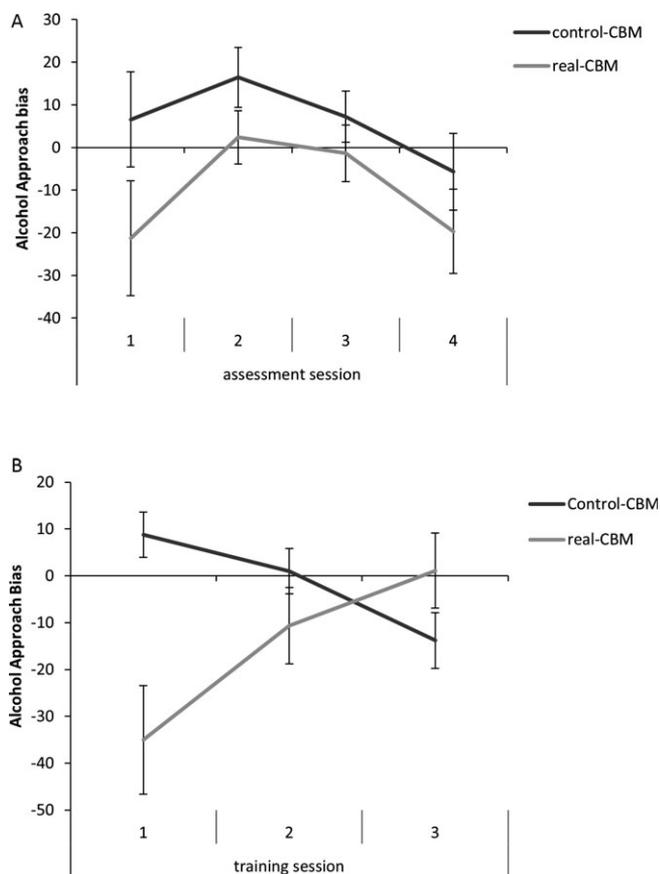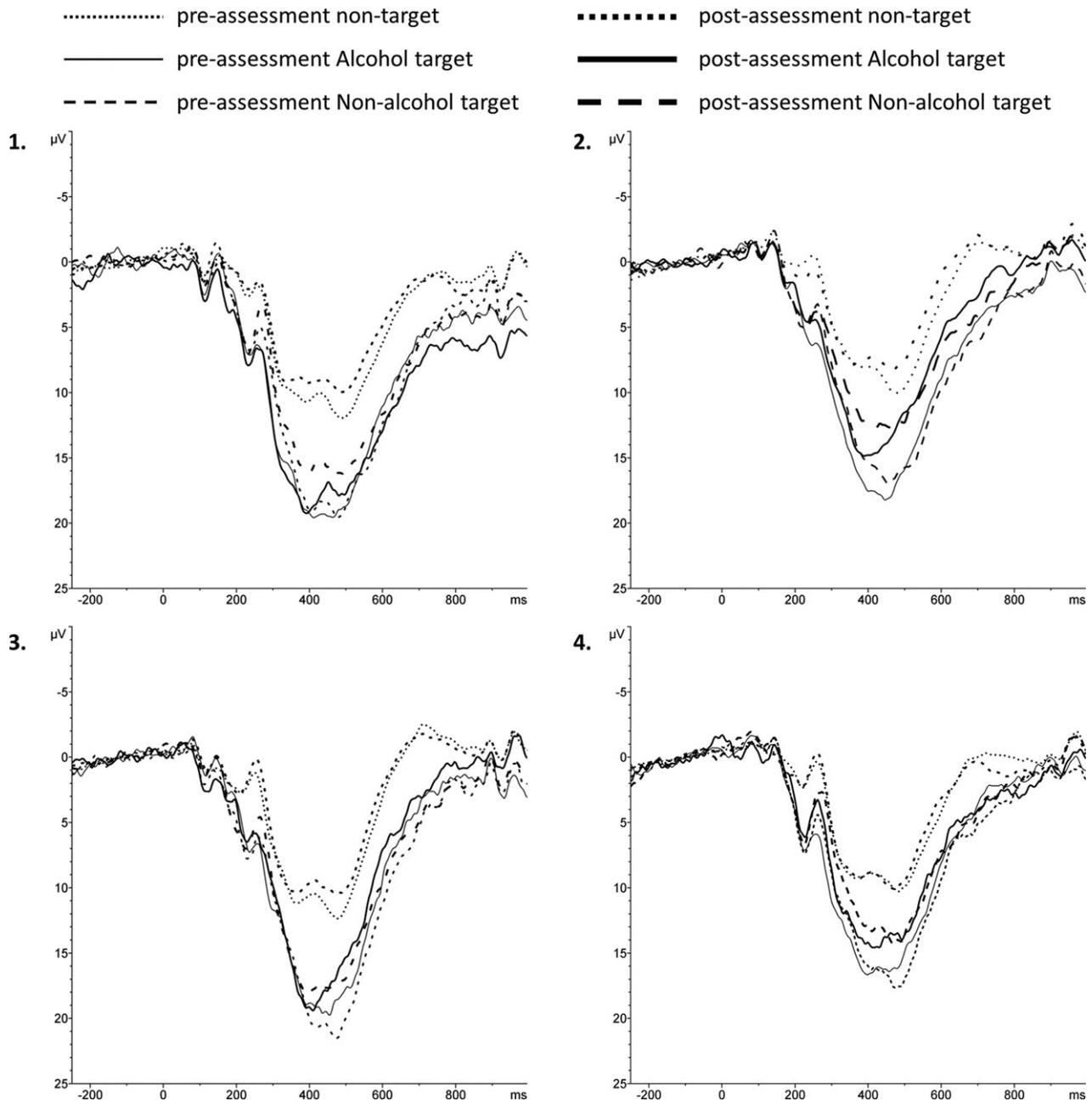**Fig. 2.** Oddball ERP. ERPs on the Pz for the oddball task separately for each group (the number corresponds with the group). 1: Sham-tDCS with control-CBM, 2: active tDCS with control-CBM, 3: sham-tDCS with active CBM, 4: active tDCS with active CBM. Light lines represent the pre-assessment and dark lines the postassessment. There is a clear oddball P300 effect visible for target (alcohol/nonalcohol) stimuli around 400 to 500 ms. CBM, cognitive bias modification; ERP, event-related potential; tDCS, transcranial direct current stimulation.

$p < 0.01$, $\eta_p^2 = 0.30$, which showed the P300 was highest at Pz (Fig. 4). There was a significant interaction with location and stimulus type, $F(1, 65) = 6.491$, $p = 0.01$, $\eta_p^2 = 0.09$, and there was a more positive peak for alcohol on the parietal electrodes and a more negative peak on the frontal electrodes; however, the separate analyses for each location were not significant ($p > 0.3$). There was a significant interaction with time, location, hemisphere, and stimulus type, $F(2, 130) = 3.54$, $p = 0.03$, $\eta_p^2 = 0.05$; the interaction was only significant for the parietal electrodes, $F(2, 65) = 3.53$, $p = 0.04$,

$\eta_p^2 = 0.10$, and not the frontal electrodes ($p = 0.16$), follow-up analysis showed that the peak for alcohol stimuli decreased over time on the Pz, $t(68) = 2.18$, $p = 0.03$, and P5, $t(68) = 2.61$, $p = 0.01$, but not on P6 ($p = 0.47$) or for nonalcohol stimuli ($p > 0.11$).

The ANOVA for the extended P300 (P3e) amplitude showed a main effect of location, $F(1, 65) = 203.58$, $p < 0.01$, $\eta_p^2 = 0.76$, and hemisphere, $F(2, 130) = 30.20$, $p < 0.01$, $\eta_p^2 = 0.32$, and a significant Location $\times$ Hemisphere interaction, $F(2, 130) = 8.58$, $p < 0.01$, $\eta_p^2 = 0.12$,
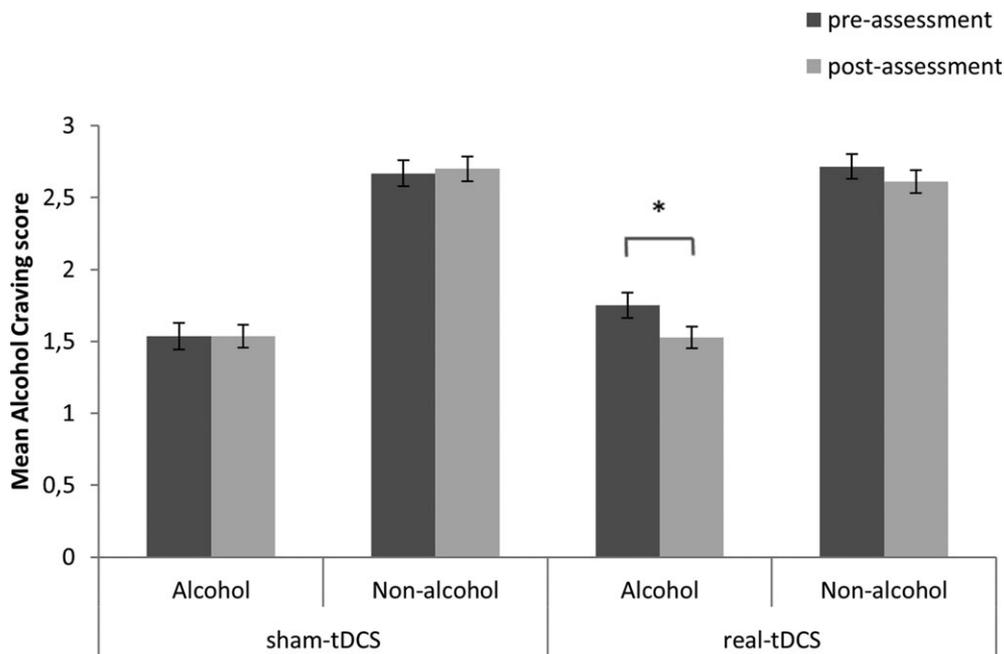
Fig. 3. Craving EEG task data. Average score for alcohol or nonalcohol pictures presented in the craving EEG task. There is a small decrease in alcohol craving from pre- to postassessment after active tDCS (*=p<0.05). Error bars represent standard error of the mean. *p < 0.05. tDCS, transcranial direct current stimulation; EEG, electroencephalogram.

which showed that the P3e was also highest at Pz. There was a main effect for stimulus type, $F(1, 65) = 5.81$, $p = 0.02$, $\eta_p^2 = 0.08$, and an interaction with location, $F(1, 65) = 8.42$, $p < 0.01$, $\eta_p^2 = 0.11$; the P3e amplitude was larger for nonalcoholic pictures and this was more pronounced at the frontal electrodes. There was a significant interaction with time, hemisphere, stimulus type, and tDCS, $F(2, 130) = 8.58$, $p < 0.01$, $\eta_p^2 = 0.12$. The effect was larger for parietal ($p = 0.09$) then frontal electrodes ($p = 0.30$), and there was a significant interaction with hemisphere and tDCS for nonalcohol stimuli, $F(2, 130) = 3.63$, $p = 0.03$, $\eta_p^2 = 0.05$, and not for alcohol stimuli ($p = 0.65$). This interaction showed that there was an small increase in peak amplitude on Pz and a decrease on P6 for sham-tDCS, and no difference for active tDCS; however, these follow-up tests for each electrode were all nonsignificant ($p > 0.34$). There was also a significant interaction with time, hemisphere, location, CBM, and tDCS, $F(2, 130) = 4.38$, $p = 0.01$, $\eta_p^2 = 0.06$, but none of the relevant follow-up analyses on location or hemisphere reached significance ($p > 0.16$).

DISCUSSION

In this study, we investigated whether tDCS could enhance an avoidance bias trained with CBM. There was a decrease in most measures over time; on average, students showed a decrease in craving, drinking, and approach bias. Several sessions of CBM did not reduce approach bias (in the AAT or IAT) at postassessment, but surprisingly, analysis of the bias scores during the second training session indicated that in both the control training and active training, no bias was

found (i.e., bias scores were around zero). In the absence of clear CBM effects, it is perhaps not surprising that we found no evidence for an enhancement of CBM due to tDCS in any of the outcome measurements. tDCS itself did not reduce craving on the inclined scale of the alcohol craving questionnaire; however, it did reduce cue-evoked craving for alcohol pictures in the EEG task. Another possibly interesting tDCS effect was that participants reported less fatigue after active stimulation. The different interventions did not affect the P300 for alcohol stimuli.

CBM did not lead to a more negative bias over time; training data showed that after the first training participants did not show a bias, that is they were as fast to approach alcohol as to avoid alcohol stimuli. It is likely that participants learned to fully ignore the contents of the picture and only responded to the task-relevant (content irrelevant) feature, the tilt of the picture, and that this reduced the efficacy of the training. However, in alcoholic patients, no significant differences were found between a relevant and irrelevant feature version of the training (Wiers et al., 2011). For future studies with a subclinical sample, it might be better to create a relevant feature training condition. Furthermore, a previous study with 2 sessions of approach bias retraining (also irrelevant feature 90 to 10%) with heavy drinking undergraduates also did not find evidence of training effects (Lindgren et al., 2015). It is likely that hazardous drinkers perform differently than alcoholic patients, as there are many differences in population characteristics, for example, the gender distribution, age, severity of impairments, and motivation to change behavior. We tried to recruit participants who wanted to reduce their drinking, but on average, motivation to change
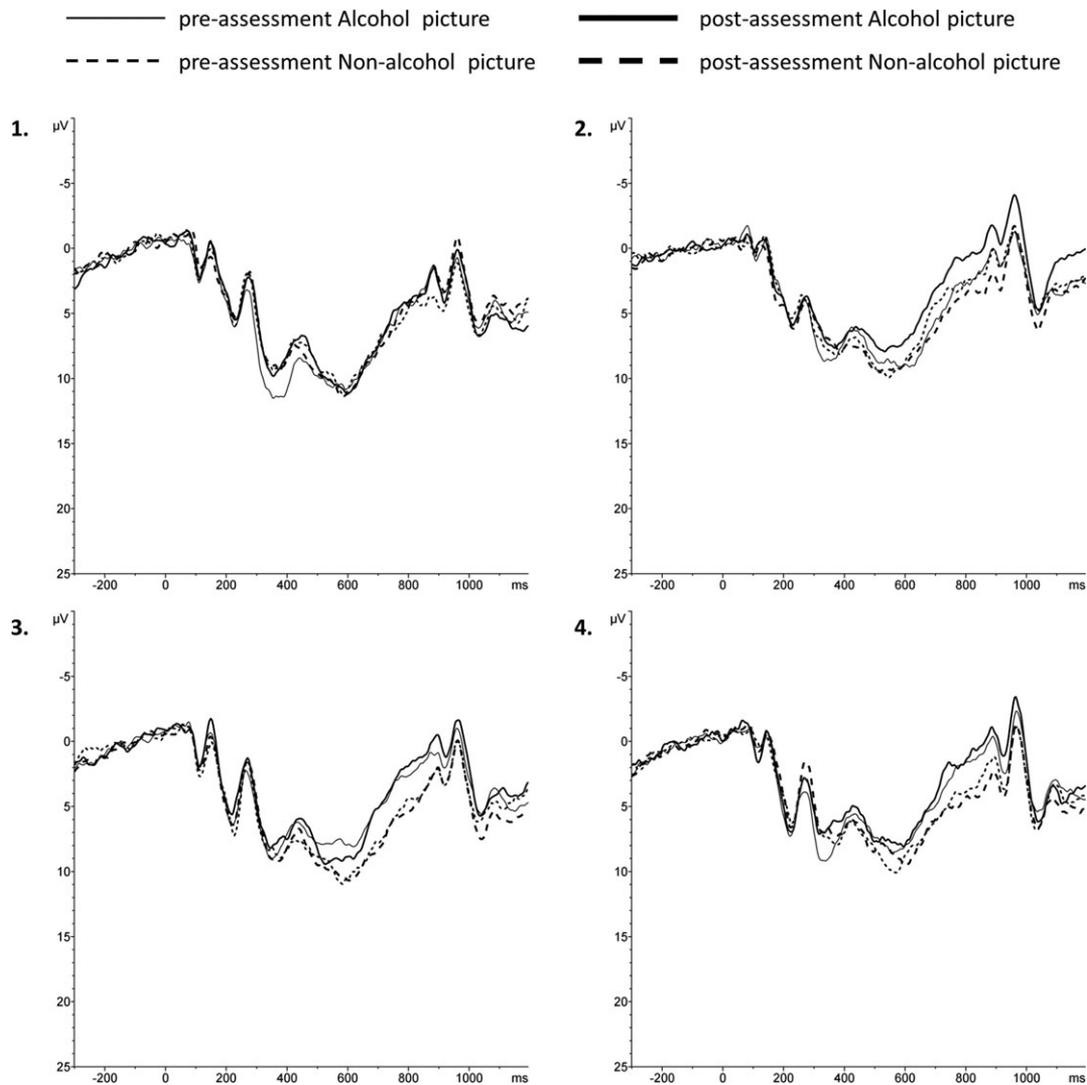
Fig. 4. Event-related potentials (ERPs) craving task. ERPs on the Pz for the cue craving task separately for each group (the number corresponds with the group). 1: Sham-tDCS with control-CBM, 2: active tDCS with control-CBM, 3: sham-tDCS with active CBM, 4: active tDCS with active CBM. Light lines represent the pre-assessment and dark lines the postassessment. CBM, cognitive bias modification; ERP, event-related potential; tDCS, transcranial direct current stimulation.

was low. Although we focused on changing automatic processes (which could occur independent of motivation), future studies might benefit from recruiting only participants with high motivation to change (Wiers et al., 2016). Students were also not asked to abstain from drinking during the period in which they performed sessions of the experiment.

With an absence of clear CBM effects, it becomes difficult to judge whether tDCS could enhance the training. Although tDCS showed no effect on reaction times during the training, it remains to be investigated whether tDCS can enhance CBM when it is successful in reversing a bias, for instance, in clinical samples. It should be noted that recent neuroimaging findings demonstrated an important role for the medial prefrontal cortex in reducing approach bias scores (Wiers et al., 2015). This area is important for encoding the motivational value of the addictive stimuli; it could be that effectiveness of CBM treatment is mostly dependent on changing the

automatic reactions toward these alcohol stimuli and less dependent on the cognitive control over these stimuli. In that case, improving cognitive and inhibitory processes in the DLPFC might not be an effective strategy to reduce this cognitive bias. Also as tDCS does not directly activate neurons, but facilitates activation, the effects are highly dependent on the activated brain networks, and if the relevant networks are not (or already optimally) activated, it might not have any effects at all.

As found in previous studies, tDCS could reduce cue-evoked craving, specifically the desire to drink presented pictures of different beverages (Boggio et al., 2008). It is likely that, especially in this nondependent sample, cue-evoked craving is a more appropriate target for craving reduction; compared to simple questions, an alcohol cue is more potent in creating a craving response and thus the potential to control it. However, these effects on craving still remain unstable

due to low craving scores and a small baseline difference. There was an interesting unexpected difference in the side effects after tDCS stimulation. The decrease in fatigue after tDCS might represent more efficient processing during the CBM task, thereby not causing an increase in fatigue. Improved efficiency or attention would not lead to a stronger bias, but it could for example, lead to improvements in working memory in long and difficult tasks, where sustained attention is important.

These specific electrophysiological measures did not provide extra information as an intervention outcome in this study. Similar as in previous research (Ceballos et al., 2012; Petit et al., 2013), a higher amplitude for the P300 peak was found for alcohol pictures on the parietal electrodes, which could indicate preferential processing of alcohol stimuli in this sample. Hazardous drinkers also responded faster to alcohol stimuli in the oddball task. An important note regarding the task is that both infrequent and frequent stimuli required a response, thus lacking the inhibitory effect typically seen in oddball tasks. The inhibitory effect might be especially relevant for finding a large difference between alcohol or nonalcohol stimuli in the physiological response. The craving task showed a similar larger P300 for alcohol stimuli on the parietal electrodes, but a higher extended P300 peak on the frontal electrodes for nonalcohol stimuli, which might be related to the larger craving response participants showed for nonalcohol stimuli. The P300 for alcohol stimuli was slightly reduced after the intervention on the central and left parietal electrodes, possibly indicating some reduced sensitivity for alcohol pictures; however, this did not differ per condition.

This study did not show that CBM has any effects in a hazardous drinking student sample, most likely due to the participants characteristics (nonabstinent and nonclinical) and/or due to the specific training (irrelevant feature). tDCS did not have any effect on CBM, either during training or on the outcome measurements. The ability of tDCS to reduce alcohol cue-evoked craving was further supported within a subclinical sample, and a beneficial effect on fatigue was unexpectedly found. Although in this sample the tDCS effects did not extend to actual drinking behavior and did not have electrophysiological consequences, it is important to note that we examined effects that occur after an intervention and not direct effects that occur immediately after CBM or tDCS. Our results support the further use of tDCS as a method to reduce alcohol craving and may help develop new ways to enhance cognitive training with tDCS.

ACKNOWLEDGMENTS

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