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A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining

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ABSTRACT

Two studies showed an improvement in clinical outcomes after alcohol approach bias retraining, a form of Cognitive Bias Modification (CBM). We investigated whether transcranial direct current stimulation (tDCS) could enhance effects of CBM. TDCS is a neuromodulation technique that can increase neuroplasticity and has previously been found to reduce craving. One hundred alcohol-dependent inpatients (91 used for analysis) were randomized into three experimental groups in a double-blind parallel design. The experimental group received four sessions of CBM while receiving 2 mA of anodal tDCS over the dorsolateral prefrontal cortex (DLPFC). There were two control groups: One received sham stimulation during training and one received active stimulation at a different moment. Treatment outcomes were abstinence duration (primary) and relapse after 3 and 12 months, craving and approach bias (secondary). Craving and approach bias scores decreased over time; there were no significant interactions with experimental condition. There was no effect on abstinence duration after three months ($\chi 2(2) = 3.53$, $p = 0.77$). However, a logistic regression on relapse rates after one year (standard outcome in the clinic, but not-preregistered) showed a trend when relevant predictors were included; relapse was lower in the condition receiving active stimulation during CBM only when comparing to sham stimulation ($B = 1.52$, S.E. = .836, $p = .07$, without predictors: $p = .19$). No strong evidence for a specific enhancement effect of tDCS on CBM was found. However, in a post-hoc analysis, tDCS combined with CBM showed a promising trend on treatment outcome. Important limitations are discussed, and replication is necessary to find more reliable effects.

Keywords alcoholism, CBM, tDCS.

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1. INTRODUCTION

Alcohol dependence is characterized by reduced self-regulation, increased cravings and frequent relapses, and is difficult to treat with treatment response rates of 40 to 60% after a year (Group PM research 1997; Koob & Volkow 2010). Two recent studies with large samples showed a beneficial effect of cognitive training aimed at retraining automatic approach reactions towards alcohol, when added to regular treatment (R.W. Wiers *et al.* 2011; Eberl *et al.* 2013). In this form of Cognitive Bias Modification (CBM), patients perform several sessions in which they repeatedly simulate pushing away alcohol, by pushing away pictures with a joystick. Relapse rates one year after treatment discharge were reduced by 13 and 9%, respectively (R. W. Wiers *et al.* 2011; Eberl *et al.* 2013), and this effect was mediated by a change in cognitive bias (Eberl *et al.* 2013; Gladwin *et al.* 2015). Although these effects are promising, one year after treatment still almost half of the patients had relapsed. Hence, there is still room for improvement. This study investigated the potential of transcranial direct current stimulation (tDCS), a brain stimulation technique that can increase plasticity (Nitsche & Paulus 2000), to augment alcohol approach bias retraining.

TDCS modulates neuronal processing via a small electrical current. The current (usually 1 to 2 mA) near the anodal electrode can increase excitability in the

underlying cortex, whereas the cathodal electrode can decrease excitability (Nitsche & Paulus 2000). These changes in excitability can facilitate or inhibit associated cognitive processes. First studies indicate that stimulating the cortex could improve cognitive training (Elmasry, Loo, & Martin 2015), making the technique of interest to CBM.

The dorsolateral prefrontal cortex (DLPFC) has been frequently targeted in research ranging from working memory (Brunoni & Vanderhasselt 2014) to depression (Nitsche *et al.* 2009), with promising results. Recent studies have also found that stimulation of the DLPFC can reduce alcohol craving (Boggio *et al.* 2008; den Uyl, Gladwin, & Wiers 2015) and tDCS sessions on five consecutive days could reduce alcohol relapse (Klauss *et al.* 2014) and amount of cigarettes smoked (Boggio *et al.* 2009). The DPLFC is involved in executive functions (e.g. planning, flexibility and goal-directed behaviour), which are related to addiction (Goldstein & Volkow 2011). Decreased craving is correlated with increases in DLPFC activation, which could be related to improvements in self-regulation (Kober *et al.* 2010). Further, alcohol stimuli induce strong craving responses in alcohol-dependent patients, and these could increase motivation to approach alcohol (Veilleux & Skinner 2015). Approach inclinations towards alcohol and craving are closely linked theoretically (Breiner, Stritzke, & Lang 1999). If stimulating the DLPFC can increase self-regulation, it could help patients to overcome automatic approach tendencies for alcohol. It should be noted that as yet studies of effects on implicit measures in heavy drinkers have not supported the hypothesis that anodal tDCS of the DLPFC can reduce such biases (Gladwin, den Uyl, & Wiers 2012, den Uyl *et al.*, 2016, den Uyl, Gladwin, & Wiers 2016). Nevertheless, tDCS could improve the efficacy of alcohol approach bias retraining in a clinical sample, e.g. by increasing the ease with which new avoidance associations are formed or by increases in cognitive control over these associations.

This study will therefore investigate whether tDCS enhances the effects of approach bias retraining, primarily by comparing the effects of four sessions of CBM with left DLPFC tDCS with four sessions of CBM with sham tDCS. In the first patient study with alcohol approach bias retraining four sessions were sufficient to influence alcohol bias and relapse (R.W. Wiers *et al.* 2011). The study is done in the same clinic as the previous two CBM studies; where, given previous positive findings, approach bias retraining is now part of regular treatment. However, because tDCS already has been found to diminish craving by itself, we wanted to control for these effects. In order to separate a main effect of tDCS from an enhancing effect on CBM, we introduced an extra control group that also received four active tDCS sessions, but not simultaneously with training. We hypothesized that combining tDCS with CBM would result in a stronger reduction of the alcohol approach bias and a stronger reduction in craving, compared to the control groups. We also hypothesized that the combination of tDCS and CBM would have a beneficial effect on treatment outcomes: length of abstinence and occurrence of relapse after three months and one year.

2. MATERIALS AND METHODS

2.1. Participants

The study was performed in the Salus clinic, Lindow in Germany, where patients received three months of inpatient treatment. Patients participated in testing between February and July 2014. Participants were recruited within the first weeks of their treatment and could participate if none of the tDCS exclusion criteria applied (exclusion criteria were: epilepsy, multiple sclerosis or other neurological illness, previous brain injury/infection, metal in the brain, pacemaker, pregnancy, claustrophobia, recent fainting/panic attack, frequent headaches or dizziness, eczema or other skin conditions). We aimed at a sample of 90, which would give reasonable power to find medium to large effects (similar to Klauss *et al.* 2014) and was considered feasible. To account for dropout, a total of 100 patients were included in the study. The analytical sample consisted of 91 patients (Fig. 1), consisting of 30 women and 61 men, mean age 47 (SD 8.8) years (Table 1). Two patients did not continue the study (without providing a reason), one patient dropped out because of the tDCS being uncomfortable, one realized later that she was not allowed to participate (because of history of epilepsy), three patients left the clinic during treatment and two were excluded after finishing the study (one because of a testing error, one did not receive standard treatment). All participants gave written informed consent. Ethical approval was received from the ethics committee of the German Pension Fund (the financer of treatment of alcohol dependence in rehabilitation clinics) and the University of Chemnitz. The trial was registered in the Dutch Clinical Trial Registry (Number: NTR4475).

2.2. Design and treatment

2.2.1. Design

This study used a double-blind design with three experimental conditions. Because approach bias retraining was a regular part of treatment, all groups received four sessions of this training, while undergoing (sham/active) tDCS. The training was initiated after the tDCS was turned on for approximately 1 minute and lasted for

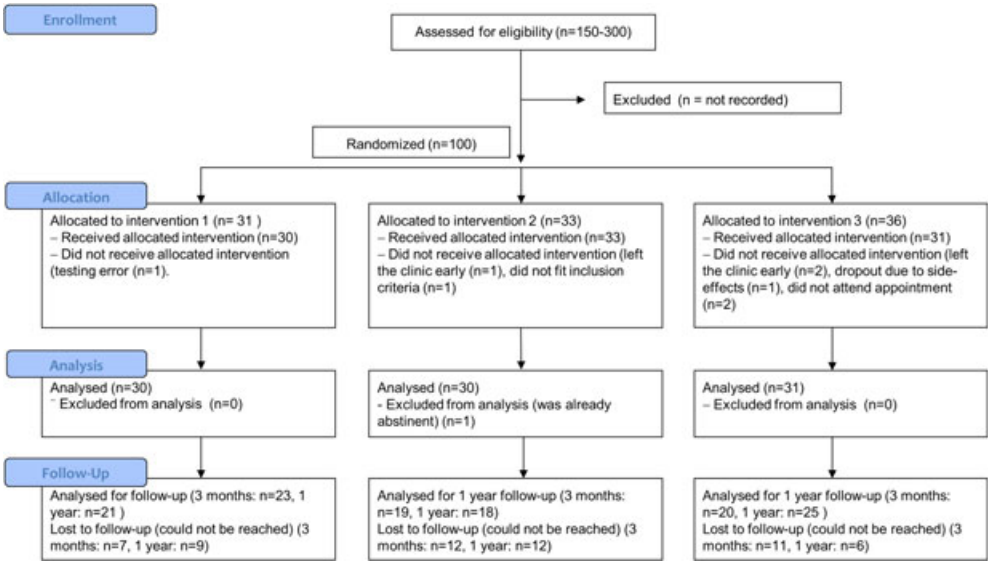

Figure 1 Flow diagram according to CONSORT 2010

Table 1 Demographic variables. Overview of the mean (M) and standard deviation (SD) of the baseline scores for all demographic variables per group. There is a difference in the amount of days in the clinic after which the participants started the study. AUDIT = Alcohol use Disorder Identification Test, BDI = Beck's Depression Index, SCL-90 = Symptom Checklist-90—Revised, PACS = Pennsylvania Alcohol Craving Questionnaire.

	1. active tDCS + CBM		*2. sham tDCS + CBM*		*3. active tDCS separate from CBM*		
	M	*SD*	*M*	*SD*	*M*	*SD*	*p*
Gender (F/M)	10/20		9/21		11/20		0.901
Smoker (Y/N)	21/9		26/4		21/10		0.241
Age (years)	49.7	9.1	46.4	8.2	46.8	9.0	0.291
Duration of alcohol problems (years)	11.3	9.0	12.8	10.4	11.0	10.3	0.623
Alcohol problems (AUDIT score)	27.5	6.5	24.0	6.2	24.3	7.3	0.086
Number of detoxifications	2.5	2.5	2.0	2.6	1.7	2.0	0.234
Duration of treatment (days)	82.0	8.0	80.1	11.0	81.1	10.8	0.765
Start experiment (days)	27.5	11.4	22.3	8.7	20.3	8.3	0.012
Depression (BDI score)	13.0	9.2	16.0	13.3	12.3	13.1	0.438
Mental burden (GSI SCL-90 score)	63.1	10.8	63.2	12.2	57.7	11.8	0.110
Craving baseline (PACS score)	7.3	5.7	5.9	5.7	4.4	5.3	0.142

15–20 minutes (depending on the speed of the participant). In order to maintain the double blind structure, all participants also received four sessions of (sham/active) tDCS while watching a neutral nature video. Hence, participants could receive active stimulation either during CBM or during the video without the patient or the experimenter knowing the condition. Participants were randomly assigned to one of three conditions: (1) Experimental intervention: active tDCS during CBM (and sham during video); (2) Active control intervention: Sham tDCS during CBM (and sham during video); and (3) Additional Active control intervention: active tDCS separate from CBM (sham tDCS during CBM, and active tDCS during video). The tDCS device had a blinding function, which used pre-programmed 5 number codes that determined whether active or sham stimulation was given. The different conditions were created by selecting the appropriate (sham/active) codes for each block; the list was subsequently randomized with the Excel rand function, so none of the involved researchers knew the group condition. The order of first receiving the block of CBM or video sessions was counterbalanced.

2.2.2. Transcranial direct current stimulation

In each session, rubber straps were attached to the head to hold the saline soaked sponges that contained the electrodes. A 35-cm^2 electrode was used over F3 (targeting left DLPFC), and a 100-cm^2 electrode was used over the F4, to approximate unilateral stimulation (Boggio *et al.*

2009). In order to reduce shunting, care was taken that the electrodes were at least 8 cm apart (by slightly adjusting the F4 electrode). The current strength was 2 mA and administered with a neuroConn DC-stimulator Plus. In order to reduce the likelihood that patients recognized the sham stimulation, a longer ramping period was used of 2 minutes (O'Connell *et al.* 2012); the fade-out time was 10 seconds. During tDCS sessions with active stimulation, the current lasted for 20 minutes (including fade-in); during sham stimulation, the current was automatically turned off after 30 seconds (after fade-in).

2.2.3. Alcohol approach bias retraining

In this task, participants were required to respond to tilted pictures of alcohol-containing beverages and of soft-drinks, with an approach or avoidance movement. In total, 16 alcohol and 16 soft-drink pictures were used. The participant was instructed to make a pull movement when the picture was tilted to the left, and to make a push movement when the picture was tilted to the right. Congruent with a pull movement, the picture became larger, suggesting approach, and with a push movement, the picture became smaller, suggesting avoidance. Participants received a training in which all alcohol pictures were presented in the push-format, and all non-alcohol pictures in the pull-format. Each training session consisted of 390 trials, which were preceded by 40 assessment trials. During assessment, the contingency of pushing or pulling alcohol or soft-drink was 50%.

2.3. Outcome measures

2.3.1. Approach avoidance task

The assessment version of the task was similar to the training version, but the contingency of pushing or pulling alcohol (or soft-drink) was 50%. The task contained 80 trials (20 per condition) and included 10 alcohol pictures and 10 soft-drink pictures. It was preceded by 12 (in the first assessment) or 4 (in the second assessment) practise trials with neutral tilted images in order to familiarize the patients with the push and pull movements in response to picture tilt.

2.3.2. Pennsylvania Alcohol Craving Questionnaire (PACS)

Craving was measured with a German translation of the PACS craving questionnaire (Flannery, Volpicelli, & Pettinati 1999), which measured overall craving in the preceding week. It included five questions on the frequency and strength of craving, with different answer options on a 0 to 6 scale, which were summed for a total score.

2.3.3. Relapse

We investigated length to relapse (primary outcome) after 3 months and occurrence of relapse after three months and one year. Patients were contacted via a letter, which was sent to them 3/12 months after discharge from the clinic, with questions regarding their frequency and latency of relapse and further treatment. If no response was given, patients were contacted via telephone. There is a discrepancy in the data we collected compared to what was in the trial registration; we have not been able to collect percentage of drinking days, because this would have required an unfeasible change in the standard follow-up procedure of the clinic. For the 3-month relapse data, relapsed was defined as more than one lapse or a lapse of more than 3 days (as in R. W. Wiers *et al.* 2011); for the one year measurement, relapse was defined by clinicians who were blind to condition, scored in accordance with the German Addiction Society (as in R. W. Wiers *et al.* 2011; Eberl *et al.* 2013). Two scores were used, complete abstinence and improvement (no more than one relapse and abstinent again for at least one month at follow-up); both were scores as success, in line with standard procedures in the clinic.

2.4. Questionnaires

2.4.1. Alcohol Use Disorder Identification Test (AUDIT)

Hazardous alcohol use was measured with a German version of the AUDIT (Saunders *et al.* 1993; Dybek *et al.* 2006). It contained 10 questions on alcohol use and problems over the last year with answer options ranging from 0 to 4 points.

2.4.2. Beck Depression Inventory (BDI)

Symptoms of depression were measured with a German version of the BDI (Beck & Steer 1993; Hautzinger *et al.* 1994). It contained 21 questions with statements on mood and feelings in the past week with answer option ranging from 0 to 3 points.

2.4.3. Symptom Checklist 90-R (SCL90-R)

Physical and psychological impairment of a person in the past week was measured with the German version of the SCL-90-R (Derogatis 1983; Franke 1995). It contained 90 questions, with answer option ranging from 0 to 4 points.

2.4.4. Adverse effects tDCS questionnaire

Possible side effects of the tDCS stimulation were assessed with an adapted version of the Adverse Effects tDCS questionnaire translated to German (Brunoni *et al.* 2011). It

contained 10 possible side effects (itching, tingling, burning, scalp pain, neck pain, headache, dizziness, sleepiness, trouble concentrating, nausea), which were scored on a 1 to 4 scale, and also included the question whether the side effect was believed to be related to tDCS (also scored on a 1–4 scale). We also added two questions on the strength of the stimulation and the uncomfortableness of the stimulation, on a scale of 1 to 10.

2.5. Procedure

After entering the clinic, patients were asked to attend an information session about the study where they received information and could decide whether they would like to participate. Patients filled out the list with exclusion criteria, which were checked by their physician. When patients entered the clinic, and again when they left, they performed a test battery to assess neuropsychological functioning. The alcohol approach bias assessment data was gathered in this 'neurocheck' test battery (which included a working memory task, Stroop task, AAT and IAT). Participants started the study sometime between their second to fifth week in the clinic. When participants were suitable and willing to participate, an appointment was made by the experimenters; during their first appointment, patients were allocated to one of the three conditions. On the first day of the experiment, they filled out the PACS,[1] then, followed the first training block of four sessions of CBM or video-presentation with tDCS stimulation. All four sessions were completed within one week, with only one training session per day. After the first block, there was a break of at least one week between the last session of block one and the first session of block two. The four sessions within block two were also performed within one week. At the beginning of block two and after block one, the PACS was administered again (for simplicity only the final assessment is included in the analysis).

2.6. Data analysis

For the continuous outcome variables (PACS, alcohol bias) with multiple measurements, we used a repeated measures ANOVA with the different time-points (before and after treatment) as within factor and Condition as between factor. In case of a large deviation of normality (PACS scores) a non-parametric test was also performed (a related sample Wilcoxon Signed rank test for time effects and a Kruskal–Wallis test on difference scores for between-subjects effects). These non-parametric outcomes were only reported if they differ in conclusion from the ANOVA. A non-parametric test was also used for length to relapse. For effect-size calculations for parametric tests, partial eta squared was used, and for non-parametric tests Cramer's V was used. For the binary relapse data, we performed automatic multiple imputation (MI, with SPSS 20) to estimate the missing values. Because we had approximately 30% missing data, we used 30 imputations (Bodner, 2008). We used all demographic variables from Table 1 and the outcome measures from Table 2 as predictors. We performed a logistic regression with complete cases and MI analysis. The same predictors as in R. W. Wiers *et al.* (2011) were entered in the first step, because this study was similar, and the predictors were relevant for relapse prediction, which allows for testing incremental variance explained in the second step (cf. Cohen et al., 2013). Condition was entered as two dummy variables in the second step. To obtain a pooled result in the MI analysis of the second step, we used the median *p*-value, which gives a good estimate of the significance of a categorical variable (personal communication with I. Eekhout). In case of a follow-up analysis, we compared two groups separately in the logistic regression.

3. RESULTS

3.1. Demographic variables

Except for one patient who did not continue the study because of side effects, the patients tolerated the stimulation well. Participants typically reported either no or small side effects and could not discern sham or active stimulation (see Supporting Information). Patients reported more side effects (such as itching, burning, sleepiness) during active stimulation, but could not differentiate between active and sham stimulation (see Supporting Information). All patients were randomly assigned to one of the three conditions; however, there was a significant baseline difference when participants started the experiment and also a trend level difference in AUDIT score. Patients in group 1 started on average a few days later then groups 2 and 3 and had a slightly higher AUDIT score (Table 1).

3.2. Alcohol bias

The data for the pre-intervention and post-intervention alcohol bias was collected separately during the neuropsychological test-battery; however, because not all patients attended this appointment, 23% of the data is missing (two missed both assessments, two missed the pre-treatment assessment, 14 missed the post-treatment assessment, two had the assessment at the wrong time).

[1] Patients also did a physiological cue-exposure measurement during this pre- or post-assessment, and a working memory task was performed before block 2 and in the post-assessment. These data are not included in this paper. Participants also filled out short mood visual analogue scales at the beginning and end of each testing day. These analyses are added in the Supporting Information.

Table 2 Intervention outcomes. Table 2a shows the results on continuous outcome measurements; craving, alcohol bias and time to relapse. The mean and standard error are given for the pre- and post-assessment, *p*-values represent outcomes of the ANOVA interaction Time × Condition. PACS = Pennsylvania Alcohol Craving Questionnaire. Table 2b shows the binary results of the relapse occurrences. Pooled estimations are shown with complete cases between brackets.

a		*1. active tDCS + CBM*		*2. sham tDCS + CBM*		*3. active tDCS separate from CBM*		
Outcome measurements		*M*	*SE*	*M*	*SD*	*M*	*SD*	*p*
Craving (PACS)	Pre-assessment	7.1	1.0	5.9	1.0	4.4	1.0	.38
	Post-assessment	5.6	1.0	4.4	1.0	4.1	1.0	
Alcohol bias	Pre-assessment	43.3	30.3	13.2	31.7	69.3	28.5	.27
	Post-assessment	−26.8	17.1	−38.7	17.9	−58.0	16.1	
Clinical (CC)	Time to relapse ($n = 17$)	5.4	1.7	7.1	1.3	6	1.4	.76

b		*1. active tDCS + CBM*		*2. sham tDCS + CBM*		*3. active tDCS separate from CBM*	
Outcome measurements		*Relapsed*	*Abstinent*	*Relapsed*	*Abstinent*	*Relapsed*	*Abstinent*
Clinical (CC)	Three months	8.1 (5)	21.9 (18)	12.1 (7)	17.9 (12)	9.7 (4)	21.3 (16)
	One year	6.4 (3)	23.6 (18)	12.0 (7)	18.0 (11)	8.2 (6)	22.8 (19)

There was a main effect of Time, $F(1,67) = 17.18$, $p < 0.01$, $\eta_p^2 = 0.204$, representing a reduction in alcohol bias from pre to post-treatment, but no interaction with Condition, $p = 0.27$, $\eta_p^2 = 0.038$ (Table 2).

To further investigate effects of tDCS on bias scores, we also analysed the short assessment before each training session. Because we wanted to compare tDCS and sham effects during CBM, the group receiving tDCS separate from CBM (of which half had already received tDCS) is excluded from this analysis. Again, a main effect of Time was found, $F(3,174) = 5.27$, $p = 0.002$, $\eta_p^2 = 0.083$, but no interaction with Condition $F(3,174) = 3.37$, $p = 0.252$, $\eta_p^2 = 0.023$. When we explored the temporal effects more closely with a simple contrast with session 1 as a reference category, there was a significant Session × Condition interaction for session 2, $F(1,58) = 4.26$, $p = 0.044$, $\eta_p^2 = 0.068$, but not for sessions 3 or 4, both $p > 0.2$ (Fig. 2).

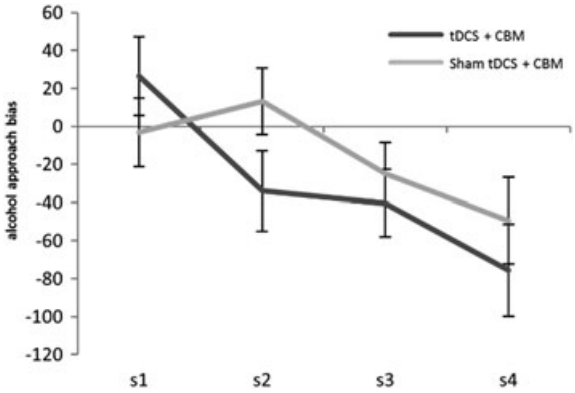

Figure 2 Alcohol bias before each training session. These represent the bias scores measured before each training session (from session 1 to season 4) with the short mini-assessment. There is a difference between condition 1 and 2 from session 1 to session 2. Error bars represent standard error of the mean

3.3. Craving

Craving decreased over Time, $F(1,87) = 7.98$, $p < 0.01$, $\eta_p^2 = 0.084$, but there was no interaction with Condition, $p = 0.38$, $\eta_p^2 = 0.022$ (Table 2). Overall craving was very low with a mean score of 5.9 (out of possible 30 points), and the scores were highly skewed (29.7% of the participants scored 0 craving at assessment 1), but non-parametric alternatives also only showed a main effect of Time.

3.4. Relapse after three months

Three-month follow-up data was obtained from 68% of the participants (Table 2b). There was no significant difference between groups in the primary outcome time to relapse $\chi^2(2) = 3.53$, $p = 0.77$, $V = 0.13$. A logistic regression was computed with the predictors gender, alcohol problems and psychopathology-related variables; in the MI analysis the median of all imputations was not significant (step 2: $\chi^2(2) = 2.49$, $p = .29$; complete case (CC) analysis: $p = .23$). AUDIT score was a trend-level significant predictor of relapse; more alcohol problems were associated with higher chance of relapse (Table 3).

3.5. Relapse after one year

One year follow-up data was obtained from 70% of the participants (Table 2b). The median of the logistic regression showed a trend-level significant effect of treatment condition (step 2: $\chi^2(2) = 5.37$, $p = .07$ (Table 3), CC analysis: $p = .07$). There were no other significant predictors of relapse. A follow-up analysis

Table 3 Logistic regression results with multiple imputation data for 3 months and 1 year. AUDIT = Alcohol use Disorder Identification Test, BDI = Beck's Depression Inventory, SCL-90 = Symptom Checklist-90—Revised, PACS = Pennsylvania Alcohol Craving Questionnaire. In condition dummy 1, the group that received tDCS simultaneous with CBM is scored as 1 and the other 2 groups as 0; in the condition dummy 2, the group that received tDCS separate from CBM is scored as 1 and the other 2 groups as 0.

		3-months relapse			*1-year relapse*		
Variable		*B*	*S.E.*	*p*	*B*	*S.E.*	*p*
Step 1	Gender	−.740	.669	.269	−.924	.733	.208
	Duration alcohol problems	−.005	.034	.890	−.016	.029	.588
	Number of detoxifications	−.149	.138	.278	.042	.149	.777
	Alcohol problems (AUDIT)	.093	.049	.060	.046	.048	.338
	Duration of treatment (days)	−.043	.030	.148	.001	.042	.984
	Depression (BDI)	.053	.052	.311	−.025	.047	.603
	SCL-90-R	−.066	.085	.439	−.024	.076	.751
Step 2	Dummy 1 tDCS simultaneous	.855	.705	.226	1.362	.801	.090
	Dummy 2 tDCS separate	.593	.693	.393	.925	.715	.196

indicated a trend level effect between the active tDCS combined with CBM group compared to the sham-tDCS group ($B = 1.52$, S.E = .836, $p = .07$, CC analysis: $p = .03$), indicating slightly less relapse after 1 year in the experimental group. However, only when controlling for other predictors, when covariates were excluded, the effect was no longer significant ($p = .19$, CC: $p = .09$). The combined and separate tDCS group comparison was not significant ($p = .68$), nor the comparison between the tDCS separately from CBM and sham-tDCS group ($p = .19$).

4. DISCUSSION

In this study, we failed to find the predicted enhancement effect of tDCS on CBM training. A promising trend was found on probability of relapse (on the one-year follow-up measure used standardly in the clinic, but not preregistered), but the hypotheses regarding the addition of tDCS to cognitive training in alcoholism treatment were not confirmed for alcohol approach bias, craving or time to relapse. In an exploratory analysis on the effect of tDCS on bias scores from training session 1 to session 2, we found a small beneficial effect, which is in line with the theoretical mechanism that tDCS would improve the rate of learning. However, this (small) effect did not persist over time, because both groups reached the same avoidance bias in session four, and there was no effect on alcohol bias pre- and post-intervention scores; the clinical relevance then is questionable. The relapse rates are promising with more patients remaining abstinent in the group that received tDCS combined with CBM. There was no difference between the groups that received tDCS in combination with or separate from CBM; it is therefore difficult to say whether this protective effect on relapse was because of active tDCS or the simultaneous application of tDCS during CBM sessions. Furthermore, the effect is not very robust, being only trend-level significant in the least biassed multiple imputation analysis, and only when covariates were taken into account. Nevertheless, enhancing plasticity in the DLPFC may have contributed to improvements in treatment retention or general improvements in regulating behaviour. In dependent patients, the DLPFC shows dysfunctional activity when regulating memory, attentional and inhibitory processes related to alcohol (Goldstein & Volkow 2011); repeated stimulation of this area may help restore its functioning (Fecteau *et al.* 2010). Better measurements need to be further investigated to find the exact underpinnings. For example, by including neuroimaging techniques which may be used to associate stronger activations in the stimulated areas during cognitive control tasks to better treatment outcome.

A limitation of the study is that there were some inconsistencies in the clinical trial registration and the execution of the study. We had originally planned (and registered) to use length of abstinence as a primary outcome measure and frequency of drinking days as secondary, because a continuous measurement could reveal more subtle effects. However, that appeared not feasible in the reality of clinical research. Further, abstinence duration has the disadvantage of only being available for the subset of patients who relapse and does not include information about the relapse distribution or severity of relapse. Experiments in a clinical setting represent several difficulties; it is also challenging to control for comorbidity, medication use and drop-out, and these implications could influence outcomes. Another limitation of the study is that only active CBM conditions were used, preventing a full factorial design involving placebo CBM. Consequently, the conclusions drawn from this study are limited to effects of tDCS manipulations given in

addition to active CBM. However, the fact that active tDCS on top of CBM and treatment as usual could still somewhat reduce relapse rates could be considered even more valuable.

A reason for the lack of findings on most behavioural measures could be because of the instruments used for the outcome measurements. Craving was very low in the sample (as is commonly found in a clinic), and therefore it was difficult to measure small fluctuations in craving. Future studies should look into more sensitive ways to measure craving and could benefit from including stronger cue-reactivity procedures to induce craving. The scores on the approach-avoidance task only showed a small effect in the training. It could be that after a certain number of sessions, participants reach a ceiling and no longer reduce their reaction times; however, this does not exclude the possibility for changes occurring in brain activity. Also, it might be that differences in cognitive tasks in a clinical sample are more likely found in accuracy rates (Dedoncker *et al.* 2016); therefore, these tasks might be too simple (with high accuracy rates) to find effects.

Regarding possible CBM enhancement effects, it is also uncertain whether tDCS was placed over the most appropriate area. Recent neuroimaging findings showed that reductions in alcohol approach bias (after CBM) were associated with reduction in activity in the medial prefrontal cortex (C.E. Wiers *et al.* 2015), and in another study with an Approach-Avoidance Task, no DLPFC activity was found in the avoid-alcohol contrast in patients versus controls (C.E. Wiers *et al.* 2014). It could be the case that the DLPFC is less relevant in these alcohol approach associations. Or it may be more relevant to stimulate the DLPFC in a different CBM paradigm, as recently it was found that tDCS caused a greater change in bias in an attention modification paradigm in anxiety (Clarke *et al.* 2014). Even if the appropriate area is targeted, there are still uncertainties surrounding tDCS, e.g. on how much current is actually reaching the brain (Kim *et al.*, 2014), and which parameters are most suitable. There is also current critique of tDCS research lacking convincing findings in neurophysiological studies (Horvath, Forte, & Carter 2014). However, this meta-analysis has also been criticized by other researchers (Antal *et al.* 2015). Furthermore, several more specific review articles have convincingly concluded that tDCS has beneficial effects (Nitsche *et al.* 2009; Brunoni & Vanderhasselt 2014; Dedoncker *et al.* 2016), so it could also be a problem in difficulties measuring the underlying effects.

This study investigated whether transcranial direct current stimulation could enhance alcohol approach bias retraining. Although the behaviour outcomes, craving and approach bias after treatment did not change because of the manipulation, an exploratory analysis showed learning efficiency was briefly enhanced by tDCS. There was a trend level beneficial effect of tDCS on relapse rates after one year in the condition that received the combination intervention, but no differentiation could be made between the best timing (concomitant or not with CBM). Although several limitations in this study warrant caution, these albeit more exploratory findings fit with previous studies that show potentially large benefits of tDCS in helping alcohol dependent patients cope with relapse (Klauss *et al.* 2014). This study provides some support for a positive view of tDCS for treatment augmentation, but more research is needed to better explore its possible effects and how best to optimize and measure them.

Author Contribution

All authors were involved in developing the experiment. The experiment was designed in detail by TdU, TG and RW. MR made the approach bias retraining task. JL was responsible for patient enrolment. TdU drafted the manuscript. TG, RW and MR provided critical revision of the manuscript. All authors approved the final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Overview of reported side-effects
Figure S2 Stimulation type blinding
Table S1 Pre and post scores for implicit association bias, working memory and mood