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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 re- duce craving. One hundred alcohol-dependent inpatients (91 used for analysis) were randomized into three experimen- tal 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 (χ2(2) = 3.53, p = 0.77). However, a logistic regression on re- lapse rates after one year (standard outcome in the clinic, but not-preregistered) showed a trend when relevant predic- tors 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 en- hancement 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 alco- hol, 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 af- ter treatment still almost half of the patients had relapsed. Hence, there is still room for improvement. This study in- vestigated the potential of transcranial direct current stimulation (tDCS), a brain stimulation technique that can increase plasticity (Nitsche & Paulus 2000), to aug- ment alcohol approach bias retraining.

TDCS modulates neuronal processing via a small elec- trical 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 con- secutive 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 improve- ments in self-regulation (Kober et al. 2010). Further, al- cohol stimuli induce strong craving responses in alcohol-dependent patients, and these could increase mo- tivation 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 im- prove 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 en- hances 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 alco- hol bias and relapse (R.W. Wiers et al. 2011). The study is done in the same clinic as the previous two CBM stud- ies; where, given previous positive ﬁndings, approach bias retraining is now part of regular treatment. However, be- cause 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 ef- fect on CBM, we introduced an extra control group that also received four active tDCS sessions, but not

simultaneously with training. We hypothesized that com- bining tDCS with CBM would result in a stronger reduc- tion 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 out- comes: length of abstinence and occurrence of relapse af- ter three months and one year.

1. MATERIALS AND METHODS
	1. Participants

The study was performed in the Salus clinic, Lindow in Germany, where patients received three months of inpa- tient treatment. Patients participated in testing between February and July 2014. Participants were recruited within the ﬁrst weeks of their treatment and could partic- ipate if none of the tDCS exclusion criteria applied (exclu- sion criteria were: epilepsy, multiple sclerosis or other neurological illness, previous brain injury/infection, metal in the brain, pacemaker, pregnancy, claustropho- bia, 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 drop- out, 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 real- ized 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 in- formed consent. Ethical approval was received from the ethics committee of the German Pension Fund (the ﬁnancer of treatment of alcohol dependence in rehabilita- tion clinics) and the University of Chemnitz. The trial was registered in the Dutch Clinical Trial Registry (Number: NTR4475).

* 1. Design and treatment
		1. Design

This study used a double-blind design with three experi- mental 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 var- iables 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 partici- pant). In order to maintain the double blind structure, all participants also received four sessions of (sham/ac- tive) tDCS while watching a neutral nature video. Hence, participants could receive active stimulation either dur- ing CBM or during the video without the patient or the experimenter knowing the condition. Participants were randomly assigned to one of three conditions: (1) Experi- mental intervention: active tDCS during CBM (and sham during video); (2) Active control intervention: Sham tDCS during CBM (and sham during video); and (3) Addi- tional 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.

* + 1. Transcranial direct current stimulation

In each session, rubber straps were attached to the head to hold the saline soaked sponges that contained the elec- trodes. A 35-cm2 electrode was used over F3 (targeting left DLPFC), and a 100-cm2 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 recog- nized 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 auto- matically turned off after 30 seconds (after fade-in).

* + 1. 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. Partic- ipants 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 as- sessment trials. During assessment, the contingency of pushing or pulling alcohol or soft-drink was 50%.

* 1. Outcome measures
		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 al- cohol pictures and 10 soft-drink pictures. It was preceded by 12 (in the ﬁrst assessment) or 4 (in the second assess- ment) practise trials with neutral tilted images in order to familiarize the patients with the push and pull move- ments in response to picture tilt.

* + 1. 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.

* + 1. 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 la- tency 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 de- ﬁned 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.

* 1. Questionnaires
		1. Alcohol Use Disorder Identiﬁcation Test (AUDIT)

Hazardous alcohol use was measured with a German ver- sion 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.

* + 1. 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.

* + 1. 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.

* + 1. Adverse effects tDCS questionnaire

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

contained 10 possible side effects (itching, tingling, burn- ing, 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.

* 1. 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 in- cluded 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 ap- pointment, 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).

* 1. 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

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.

effects and a Kruskal–Wallis test on difference scores for between-subjects effects). These non-parametric out- comes 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 paramet- ric 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 imputa- tion (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 lo- gistic 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.

1. RESULTS
	1. Demographic variables

Except for one patient who did not continue the study be- cause 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 stimula- tion (see Supporting Information). Patients reported more side effects (such as itching, burning, sleepiness) during active stimulation, but could not differentiate between ac- tive and sham stimulation (see Supporting Information). All patients were randomly assigned to one of the three conditions; however, there was a signiﬁcant baseline dif- ference 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).

* 1. Alcohol bias

The data for the pre-intervention and post-intervention alcohol bias was collected separately during the neuro- psychological test-battery; however, because not all pa- tients 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).

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 inter- action Time × Condition. PACS = Pennsylvania Alcohol Craving Questionnaire. Table 2b shows the binary results of the relapse occur- rences. Pooled estimations are shown with complete cases between brackets.

1. 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 |

1. 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, ηp2 = 0.204, representing a reduction in alco- hol bias from pre to post-treatment, but no interaction

2

with Condition, p = 0.27, ηp

= 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 ex- cluded from this analysis. Again, a main effect of Time was found, F(3,174) = 5.27, p = 0.002, ηp2 = 0.083, but no interaction with Condition F(3,174) = 3.37, p = 0.252, ηp2 = 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, ηp2 = 0.068, but not for sessions 3 or

4, both p > 0.2 (Fig. 2).

* 1. Craving

Craving decreased over Time, F(1,87) = 7.98, p < 0.01, ηp2 = 0.084, but there was no interaction with Condition, p = 0.38, ηp2 = 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.

* 1. 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 χ2(2) = 3.53, p = 0.77, V = 0.13. A logistic regression was

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 be- tween condition 1 and 2 from session 1 to session 2. Error bars rep- resent standard error of the mean

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: χ2(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).

* 1. 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: χ2(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 Identiﬁca- tion Test, BDI = Beck’s Depression Inventory, SCL-90 = Symptom Checklist-90—Revised, PACS = Pennsylvania Alcohol Craving Ques- tionnaire. 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).

1. 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 per- sist 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 impu- tation analysis, and only when covariates were taken into account. Nevertheless, enhancing plasticity in the DLPFC may have contributed to improvements in treatment re- tention or general improvements in regulating behaviour. In dependent patients, the DLPFC shows dysfunctional activity when regulating memory, attentional and inhib- itory processes related to alcohol (Goldstein & Volkow 2011); repeated stimulation of this area may help restore its functioning (Fecteau et al. 2010). Better measure- ments need to be further investigated to ﬁnd the exact underpinnings. For example, by including neuroimaging techniques which may be used to associate stronger acti- vations in the stimulated areas during cognitive control tasks to better treatment outcome.

A limitation of the study is that there were some in- consistencies in the clinical trial registration and the exe- cution of the study. We had originally planned (and registered) to use length of abstinence as a primary out- come measure and frequency of drinking days as second- ary, because a continuous measurement could reveal more subtle effects. However, that appeared not feasible in the reality of clinical research. Further, abstinence du- ration has the disadvantage of only being available for the subset of patients who relapse and does not include infor- mation about the relapse distribution or severity of re- lapse. Experiments in a clinical setting represent several difﬁculties; it is also challenging to control for comorbid- ity, 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 there- fore it was difﬁcult to measure small ﬂuctuations in crav- ing. 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 cer- tain 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 accu- racy 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 appro- priate area. Recent neuroimaging ﬁndings showed that reductions in alcohol approach bias (after CBM) were as- sociated with reduction in activity in the medial prefron- tal 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 asso- ciations. 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 at- tention 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 convinc- ing 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 ef- fects (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 be- cause of the manipulation, an exploratory analysis

showed learning efﬁciency was brieﬂy enhanced by tDCS. There was a trend level beneﬁcial effect of tDCS on re- lapse 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 ben- eﬁts 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 ex- plore 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 manu- script. 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