A Clinical Trial with Combined Transcranial Direct Current Stimulation and Attentional Bias Modification in Alcohol-Dependent Patients

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A Clinical Trial with Combined Transcranial Direct Current Stimulation and Attentional Bias Modification in Alcohol-Dependent Patients

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Background: Modifying attentional processes with attentional bias modification (ABM) might be a relevant add-on to treatment in addiction. This study investigated whether influencing cortical plasticity with transcranial direct current stimulation (tDCS) could increase training effects. tDCS could also help alcohol-dependent patients to overcome craving and reduce relapse, independent of training. These approaches were combined to investigate effects in the treatment of alcoholism.

Methods: Ninety-eight patients (analytical sample = 83) were randomly assigned to 4 groups in a 2-by-2 factorial design. Patients received 4 sessions of ABM (control or real training) combined with 2 mA tDCS (active: 20 minutes or sham: 30 seconds) over the left dorsolateral prefrontal cortex. Alcohol bias and craving were assessed, and treatment outcome was measured as relapse after 1 year.

Results: Attentional bias scores indicated that during the training only the group with active tDCS and real ABM displayed an overall avoidance bias ($p < 0.05$). From pre- to postassessment, there were no main or interaction effects of tDCS and ABM on the bias scores, craving, or relapse ($p > 0.2$). However, effects on relapse after active tDCS were in the expected direction.

Conclusions: There was no evidence of a beneficial effect of tDCS or ABM or the combination. Whether the absence of effect was due to issues with the outcome measurements (e.g., lack of craving, high dropout, and unreliable measurements) or aspects of the intervention should be further investigated.

Key Words: Transcranial Direct Current Stimulation, Cognitive Bias Modification, Addiction, Alcohol.
specific effects on biases and a significantly reduced relapse rate for both types of training a year after treatment discharge (Rinck et al., in press).

There is currently debate on the effectiveness of CBM and ABM methods (Christiansen et al., 2015; Cox et al., 2014; Cristea et al., 2016; Macleod, 2012; Wiers et al., 2018), also with regard to anxiety research, a field where ABM has been tested more extensively (Beard, 2011; Clarke et al., 2014b; Cristea et al., 2015; Emmelkamp, 2012; Mogoase et al., 2014). Regarding anxiety, MacLeod and Grafton (2016) have demonstrated that beneficial clinical results have consistently been found in anxiety studies when ABM successfully changed the bias, and no effects were found when ABM did not result in a change in bias. It is therefore relevant to further investigate ABM in a clinical sample and examine whether these bias-changing effects can be improved. In the field of addiction, a meta-analysis combined proof-of-principle studies in students not motivated to change with clinical randomized controlled trials (RCTs) and “cast serious doubts on the clinical utility of CBM interventions for addiction problems” (Cristea et al., 2016, p. 2). However, once the apples (proof-of-principle experimental studies) and oranges (RCTs in clinical samples) were separated, the picture became clear: with small short-lasting effects of CBM on immediate outcome measures (e.g., a taste test) in students in case the bias was successfully manipulated (as in anxiety), and consistent small but clinically meaningful add-on effect of CBM to regular treatment in RCTs in clinical samples, with effect sizes approximately the same size as medication (Wiers et al., 2018). Here, we tested whether the effects of ABM could be augmented by stimulating relevant neural networks.

An attentional bias toward alcohol can be explained by incentive sensitization, a neural process in which the neural activity underlying the incentive value of stimuli becomes more responsive to addictive substances after repeated use (Robinson and Berridge, 1993). From an evolutionary perspective, it makes sense that rewarding stimuli rapidly grab attention (Chelazzi et al., 2013; Theeuwes and Belopolsky, 2012). An attentional bias may play a role in the maintenance of addiction and may hinder recovery. The relation between attentional bias and dependence-related processes such as relapse and craving is complex: Relapse predictions showed rather inconsistent findings (Christianen et al., 2015), and a meta-analysis showed only a modest relation to craving (Field et al., 2009). This could also be due to the measurement issues; for example, craving is complex and difficult to measure (Breiner et al., 1999), and the assessment of attentional bias is often unreliable (Ataya et al., 2012). Neuroimaging studies show that subcortical brain regions, such as the amygdala, play a significant role in triggering attentional processes (Vuilleumier, 2005). The lateral prefrontal cortex is involved in controlling attention over emotional stimuli, and the lack of control over an attentional bias might be related to impairments in these regions (Arnsten and Rubia, 2012; Bishop, 2009; Browning et al., 2010).

Clarke and colleagues (2014a) found that sending a small electrical current through the left dorsolateral prefrontal cortex (DLPFC) with transcranial direct current stimulation (tDCS) could help modulate attentional bias in highly anxious participants. Anodal stimulation, which is believed to increase excitability under the electrode (whereas cathodal decreases excitability), increased bias acquisition. A similar study found no effect on reaction time measures of attentional bias, but did find that anodal stimulation combined with ABM reduced fixation on angry faces (Heeren et al., 2015). Although the exact underlying mechanisms of tDCS are still under investigation, anodal tDCS is used to increase efficiency and plasticity in the underlying cortical area (Medeiros et al., 2012; Nitsche and Paulus, 2000; Rahman et al., 2013), increase cognitive performance (Hill et al., 2016; Nitsche and Paulus, 2000, 2011), and enhance effects of cognitive training (Elmasry et al., 2015). Adding tDCS to the ABM training might increase the effect of modifying the alcohol bias and thus provide a valuable addition to alcohol dependence treatment. Stimulation of the DLPFC (either left or right) without any simultaneous task or training has previously been used to reduce craving (meta-analysis: Jansen et al., 2013); furthermore, there are initial results indicating that it can be used to reduce relapse (Klauss et al., 2014). A previous study combining tDCS with an alcohol preference bias retraining also showed a trend-level effect on relapse, although it did not lead to a stronger bias at posttest (den Uyl et al., 2017). Modulating approach bias with tDCS in a heavy drinking population was also not successful (den Uyl et al., 2016). In this study, we want to investigate whether tDCS can have an effect on ABM training and craving in a clinical setting with alcohol-dependent inpatients.

We tested whether 4 sessions of ABM (control vs. real) training combined with 2 mA anodal DLPFC tDCS (sham vs. active) had beneficial effects on behavior and clinical measures in alcohol-dependent inpatients. We hypothesize that those patients who received tDCS stimulation while doing ABM training would develop stronger avoidance for alcohol-related stimuli and demonstrate a reduction in craving. We also expected, similar to den Uyl and colleagues 2017, where we found a trend-level effect of tDCS on relapse, that tDCS would benefit relapse prevention and that this effect may be more pronounced in the ABM training group.

MATERIALS AND METHODS

Participants

Inpatients were recruited from the Salus Clinic in Lindow, Germany, where inpatient treatment takes an average of 3 months. Patients were included in the study from December 2014 to June 2015. Participants were allowed to participate in the study if none of the tDCS exclusion criteria applied (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). Based on previous studies and feasibility, we aimed for a sample of 100 participants (Klauss et al., 2014). Ninety-eight patients were included in the study (Fig. 1), 13 dropped out during
testing (10 no reason/no further motivation, 1 due to craving, 1 due to relapse, and 1 due to an inclusion error), and 2 were later excluded (1 was analphabetic and 1 had a primary diagnosis of gambling addiction). The final analytical sample consisted of 83 patients (23 women and 60 men), with an average age of 48.6 years (Table 1). All patients gave written informed consent, and the study was approved by the Ethical Committee of the German Pension Fund and the University of Chemnitz. The trial was registered in the Dutch Clinical Trial Registry (NTR5016).

**Design and Intervention**

**Design.** We used a 2-by-2 double-blind factorial design (control vs. real ABM and sham vs. active tDCS). Patients were randomly assigned to 1 of the 4 experimental groups. The tDCS device (NeuroConn DC-stimulator Plus; neuroCare Group GmbH, Ilmenau, Germany) had a function incorporated that could apply sham or active stimulation with predetermined codes. In the script for the ABM training, a function was also incorporated to determine control or real ABM with predetermined codes. The codes that determined the placebo or real training variety for each group were covertly randomized within an Excel list with the rand function. The training consisted of 4 sessions of ABM training (control or real) during which patients received either sham or active tDCS.

**Transcranial Direct Current Stimulation.** The 2 mA stimulation was given through saline-soaked sponges that contained the electrodes, which were attached to the head with rubber straps.

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**Table 1. Demographic Variables**

<table>
<thead>
<tr>
<th>Group</th>
<th>M</th>
<th>SE</th>
<th>M</th>
<th>SE</th>
<th>M</th>
<th>SE</th>
<th>M</th>
<th>SE</th>
<th>M</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>5/17</td>
<td>4/16</td>
<td>5/15</td>
<td>7/14</td>
<td>21/62</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker (Y/N)</td>
<td>13/9</td>
<td>16/4</td>
<td>17/3</td>
<td>14/7</td>
<td>60/23</td>
<td>0.22</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.23</td>
<td>1.93</td>
<td>48.65</td>
<td>1.63</td>
<td>49.20</td>
<td>1.98</td>
<td>48.38</td>
<td>2.06</td>
<td>48.60</td>
<td>0.94</td>
<td>0.99</td>
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<tr>
<td>Duration of alcohol problems (years)</td>
<td>18.15</td>
<td>2.28</td>
<td>15.37</td>
<td>2.31</td>
<td>16.80</td>
<td>2.89</td>
<td>19.00</td>
<td>2.44</td>
<td>17.37</td>
<td>1.23</td>
<td>0.75</td>
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<td>Alcohol problems (AUDIT score)</td>
<td>27.27</td>
<td>1.66</td>
<td>23.70</td>
<td>1.52</td>
<td>24.40</td>
<td>1.47</td>
<td>26.00</td>
<td>1.50</td>
<td>25.40</td>
<td>0.77</td>
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<td>Number of detoxifications</td>
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<td>1.80</td>
<td>0.77</td>
<td>2.80</td>
<td>0.79</td>
<td>3.71</td>
<td>1.12</td>
<td>3.11</td>
<td>0.52</td>
<td>0.43</td>
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<td>Duration of treatment (days)</td>
<td>80.59</td>
<td>2.53</td>
<td>80.30</td>
<td>3.78</td>
<td>75.10</td>
<td>4.30</td>
<td>73.43</td>
<td>3.70</td>
<td>77.39</td>
<td>1.80</td>
<td>0.38</td>
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<tr>
<td>Start experiment (days)</td>
<td>10.68</td>
<td>1.05</td>
<td>11.30</td>
<td>1.22</td>
<td>10.00</td>
<td>1.11</td>
<td>12.62</td>
<td>1.49</td>
<td>11.16</td>
<td>0.61</td>
<td>0.49</td>
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<tr>
<td>Depression (BDI score)</td>
<td>14.27</td>
<td>2.67</td>
<td>12.57</td>
<td>2.41</td>
<td>11.10</td>
<td>2.96</td>
<td>12.52</td>
<td>2.33</td>
<td>12.66</td>
<td>1.28</td>
<td>0.86</td>
</tr>
<tr>
<td>Mental burden (GSI SCL-90-R score)</td>
<td>58.18</td>
<td>3.44</td>
<td>58.27</td>
<td>3.05</td>
<td>57.40</td>
<td>3.20</td>
<td>58.33</td>
<td>3.21</td>
<td>58.05</td>
<td>1.59</td>
<td>1.00</td>
</tr>
<tr>
<td>Craving baseline (PACS score)</td>
<td>3.59</td>
<td>0.68</td>
<td>2.95</td>
<td>0.64</td>
<td>5.45</td>
<td>1.26</td>
<td>4.38</td>
<td>1.08</td>
<td>4.08</td>
<td>0.48</td>
<td>0.30</td>
</tr>
</tbody>
</table>

AUDIT, Alcohol Use Disorders Identification Test; ABM, attentional bias modification; BDI, Beck Depression Inventory; GSI, global severity index; SCL-90-R, Symptom Checklist-90—Revised; PACS, Penn Alcohol Craving Scale; tDCS, transcranial direct current stimulation.

Overview of the mean (M) and standard deviation (SD) of the baseline scores for all demographic variables per group. The p-values represent outcomes of an ANOVA with group as between-subject variable.
35 cm² anodal electrode was positioned over the F3 (10 to 20 
 electroencephalogram [EEGI] location used for left DLPFC), 
 and the 100 cm² cathodal electrode was positioned over the F4. 
 A 100 cm² cathodal electrode was used to approximate unilateral 
 stimulation (Boggio et al., 2008; den Uyl et al., 2017). To reduce 
 shunting, we aimed for a 8 cm gap between electrodes (by slightly 
 adjusting the F4 electrode). When giving active stimulation, the 
 device was turned on for 20 minutes, and for sham stimulation, 
 the active stimulation was automatically turned off after 30 seconds 
 (while the display was still on). A fade-in period of 30 seconds and a 
 fade-out period of 10 seconds were used.

Attentional Bias Modification. In this task, participants were 
 required to respond to probes (arrows pointing up or down), which 
 appeared on the location of 1 of the preceding pictorial stimuli. 
 The trial started with a fixation cross (with a variable interstimulus 
 interval [ISI]) between 500 and 1,000 ms, followed by 2 pictures on the 
 left and right of the screen presented for 500 ms. These 2 pictures 
 were followed by an arrow on 1 of the 2 locations. For upward 
 arrows, participants were required to press the G of the keyboard, 
 for downward arrows the B, and the probe remained on the screen 
 until a response was given. The attentional bias task was made simi-
 lar to Zvielli and colleagues (2014) and also included trials on which 
 the target was absent and surprise trials. The 2 stimuli were either 
 alcohol and nonalcohol beverages, or in some cases 2 nonalcohol 
 beverages (absent target), or 2 objects (surprise trial). In the training 
 version, the probe appeared after the alcohol stimulus in 9 of 12 
 trials, and the probe appeared after the alcohol stimulus in 1 of 12 
 trials (contingency probe after nonalcohol vs. probe after alcohol: 
 90 to 10%); in the control version of the training, the contingency 
 was kept equivalent (5/12 probe after alcohol and 5/12 probe after 
 nonalcohol). In 1 of 12 trials, the 2 stimuli were both nonalcohol, 
 and in another 1 of 12 of the trials, the 2 stimuli were both objects. 
 The trials with objects were surprise trials, to increase the semantic 
 processing of the pictures, and required a different response (press-
 ing the space bar; Zvielli et al., 2014). For the trials with alcohol 
 and nonalcohol stimuli, 16 alcohol and 16 nonalcohol stimuli were 
 used, and 16 different nonalcohol images were used for the absent 
 target trials. The pictures were matched for color (e.g., vodka with 
 water) and composition (e.g., the presence of a glass/person). Local 
 beverages were used, and the images were shot according to the pro-
 tocol from Pronk and colleagues (2015). Each training session con-
 sisted of 468 trials, which took approximately 15 to 20 minutes 
 (depending on the reaction time of the participant). When the train-
 ing was completed before the 20 minutes of tDCS, the participant 
 remained seated until the stimulation time was also finished.

Outcome Measures

Alcohol VPT. The design of the VPT was similar to the ABM 
 training, only with equal amounts of alcohol, nonalcohol, and absent 
 target trials (36 trials each), and it included 12 surprise trials. The first 
 session was preceded by 20 practice trials to familiarize participants 
 with the task. We calculated the original attentional bias score by 
 subtracting average reaction times (only for accurate trials, and out-
 liers >3 SD were deleted) for the congruent (alcohol target) trials 
 from the incongruent (nonalcohol target) trials. Reliability scores 
 were calculated by taking the split-half (first half vs. second half) and the 
 test–retest (preassessment vs. postassessment) correlations.

Implicit Association Task. Transfer in approach and avoidance 
 associations was measured with a 7-block Implicit Association Task 
 (IAT; Ostafin and Palfai, 2006). Words were presented in the center 
 of the screen and were categorized into a category shown on the left 
 or right bottom of the screen (with k or d of the keyboard). Target 
 categories were alcohol (e.g., beer) or nonalcohol (e.g., cola), and 
 attribute categories were approach (e.g., grab) or avoid (e.g., push 
 away). Each attribute categories were shown together in 1 block to 
 measure the speed to categorize alcohol with approach (and nonal-
 cohol with avoid) and vice versa. The blocks were organized into 
 target category practice (block 1, 24 trials), attribute category prac-
 tice (block 2, 24 trials), combined approach-alcohol (practice block 
 3, 24 trials, test block 4, 48 trials), reversed target category practice 
 (block 4, 24 trials), and combined avoid-alcohol (practice block 3, 
 24 trials; test block 4, 48 trials). The reaction times for the congruent 
 block (approach-alcohol) were subtracted from the incongruent 
 block (avoid-alcohol) to form an alcohol bias score. As order effects 
 can be asymmetrical, all subjects received the same order to increase 
 predictive validity (Perugini et al., 2010).

Craving. Craving during the previous week was measured with 
 the Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999), 
 which included 5 questions (with a 6-point scale) on severity and fre-
 quency of craving in the previous week.

Relapse. We investigated relapse with standard follow-ups that 
 were gathered by the clinic. One year after discharge, patients were 
 contacted by the clinic via letter, and in case of no response via 
 phone. Clinicians who were blind to the study conditions used 3 dif-
 ferent scores in accordance with the German Addiction Society: 
 continued abstinence, improvement (where a lapse may have 
 occurred, but the last month a patient had been abstinent again), 
 and 1 for relapse without improvement. In our analyses, we used a 
 binary scoring with improvement and abstinence together as a suc-
 cess, equivalent to previous research (den Uyl et al., 2017).

Questionnaires

Alcohol Use Disorders Identification Test. The Alcohol Use Dis-
 orders Identification Test (AUDIT) was used to measure hazardous 
 alcohol use (Dybek et al., 2006; Saunders et al., 1993). The score 
 can be between 0 and 40 (sum of 10 questions), with higher scores 
 representing heavier use/problems in the last year.

Beck Depression Inventory. The Beck Depression Inventory 
 (BDI) contained 21 questions to measure depressive feelings in the 
 past week with answer options ranging from 0 to 3 points (Beck and 
 Steer, 1993; Hautzinger et al., 1994).

Symptom Checklist-90—Revised. The Symptom Checklist-90— 
 Revised (SCL-90-R) contained 90 questions (answers from 0 to 4) 
 and measured physical and psychological impairment of a person in 
 the past week (Derogatis, 1983; Franke, 1995). We used the average 
 score (global severity index) as a general indication.

Adverse Effects tDCS Questionnaire. Side effects of the stimu-
 lation were assessed with a questionnaire that checked 10 possible side 
 effects (itching, tingling, burning, scalp pain, neck pain, headache, 
 dizziness, sleepiness, trouble concentrating, and nausea). Answers 
 could be given from 0 (not present) to 3 (strongly present). We also 
 included 2 questions on the estimated strength and the uncomfort-
 ableness of the stimulation, on a 10-point scale.

Procedure

When entering the clinic, alcohol-dependent patients were invited 
 to an information session on the experiment, those willing and able 
 (inclusion criteria were checked with the physician) made appoint-
 ments to participate in the study. During the first appointment, 
 patients were randomly assigned to 1 of the 4 groups and gave writ-
 ten informed consent. During the pre- or postassessment sessions, 
 patients filled out the PACS (at the beginning) and picture ratings 
 (at the end) and performed several experimental tasks (in this order: 
 alcohol VPT, alcohol memory task, IAT, self-ordered pointing task)
and a cue-reactivity task with physiological measurements. The first training session was started directly after the preassessment. The 4 training sessions were performed within 1 week. The postassessment was made at least 1 day and maximum 7 days after the last training session (with 1 exception, due to illness 1 patient had the postassessment 10 days after the last training session).

Data Analysis

Baseline group differences in demographics and questionnaires (AUDIT, SCL-90-R, BDI) are entered in a multivariate analysis of variance (MANOVA), and ANOVA comparisons for each variable with the group as between-subject variable are reported. The PACS scores were analyzed with nonparametric tests. An effect of time with the group as between-subject variable are reported. The PACS variance (MANOVA), and ANOVA comparisons for each variable (AUDIT, SCL-90-R, BDI) are entered in a multivariate analysis of variance (MANOVA; Wilcoxon signed rank test). The postassessment 10 days after the last training session (with 1 exception, due to illness 1 patient had the postassessment 10 days after the last training session).

### Table 2. Intervention Outcomes. Results on Outcome Measurements, Craving, Alcohol Bias Measures, and Relapse. (A) The Mean and Standard Error is Given for the Pre- and Postassessment, and $p$-Values Represent Outcomes of the ANOVA Interaction Time × ABM × tDCS (or Nonparametric Test on Difference Score for PACS). (B) For Relapse Rates, the Multiple Imputation Estimates Are Given with Complete Case Results Between Parentheses

<table>
<thead>
<tr>
<th></th>
<th>1. Control ABM + sham tDCS</th>
<th>2. Control ABM + active tDCS</th>
<th>3. Real ABM + sham tDCS</th>
<th>4. Real ABM + active tDCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>SE</td>
<td>$M$</td>
<td>SE</td>
</tr>
<tr>
<td><strong>A. Outcome measurements</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Craving (PACS)</td>
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<tr>
<td>Preassessment</td>
<td>3.6</td>
<td>0.9</td>
<td>3.0</td>
<td>1.0</td>
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<tr>
<td>Postassessment</td>
<td>3.3</td>
<td>0.8</td>
<td>2.7</td>
<td>0.8</td>
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<td>Attentional bias</td>
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<tr>
<td>Preassessment</td>
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<td>6.9</td>
<td>−6.2</td>
<td>6.2</td>
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<tr>
<td>Postassessment</td>
<td>3.5</td>
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<td>3.0</td>
<td>6.9</td>
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<tr>
<td>Preassessment</td>
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<td>Postassessment</td>
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<td><strong>B. Outcome measurements</strong></td>
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<td>Relapse after 1 year</td>
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<td>Relapse</td>
<td>9.0</td>
<td>(5)</td>
<td>13.0</td>
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<td>Success</td>
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</table>

ABM, attentional bias modification; PACS, Penn Alcohol Craving Scale; tDCS, transthoracic direct current stimulation. The $p$-values represent outcomes of a chi-square test.

All patients tolerated the stimulation well, and there were no differences in reported side effects between sham stimulation and active stimulation (see Appendix S1). There was no difference in how often people thought they had received real stimulation if they were in sham or active tDCS group, $\chi^2(4) = 4.5$, $p = 0.35$. There were no significant differences between any of the baseline variables (Table 1).

### Attentional Bias

The attentional bias score showed poor split-half correlations ($r = −0.07$) and a poor test–retest correlation ($r = 0.15$). The bias score at baseline did not correlate with alcohol problems ($r = −0.04$) or craving ($r = −0.06$). The accuracy on the ABM task in the preassessment was very high (mean: 96.7%, SD = 3.7), except for 2 participants who had only 50% accuracy rates in the first session and were therefore deleted from the analysis. In the ANOVA on the bias scores with time (pre- and postassessment) and experimental group (control/real ABM and sham/active tDCS), there were no significant interactions ($p > 0.46$, Table 2). There was a main effect of time, $F(1, 77) = 4.03$, $p = 0.048$, $\eta^2 = 0.05$, the overall bias went from a slight avoidance (1-sample $t$-test: $M = −8.03$, $p = 0.06$) to more neutral at postassessment ($M = 0.54$, $p = 0.59$).

We also analyzed the attentional bias during training. An ANOVA with time (4 sessions) was run for the different attentional bias scores (due to infrequent alcohol-target trials, this could also be done for the real ABM training). The bias score showed no significant within-subject main effects or interactions with group ($p > 0.15$); however, a significant
between-subject effect was found for ABM, $F(1, 79) = 4.87$, $p = 0.03$, $\eta^2 = 0.06$, and for the interaction between tDCS and ABM, $F(1, 79) = 4.17$, $p = 0.04$, $\eta^2 = 0.05$. Bonferroni-controlled comparisons indicated that on average (4 training sessions combined) there was only a negative alcohol bias (faster when the target was behind the nonalcohol target), for those in the group that received both real ABM and active tDCS compared to the other groups (group 4 vs. group 1, $p = 0.046$, vs. group 2, $p = 0.02$, vs. group 3, $p = 0.08$; Fig. 2).

Implicit Alcohol Approach Association

The IAT approach association score showed good split-half correlations ($r = 0.83$) and good test–retest correlations ($r = 0.72$). The baseline score did not correlate with alcohol problems ($r = -0.09$) or craving ($r = 0.14$). An ANOVA on the bias scores with time (preassessment and postassessment), tDCS, and ABM did not give any significant main or interaction effects ($p > 0.44$, Table 2). The overall bias was slightly negative at baseline, in the direction of an avoidance association, but this was not significant ($M = -52.5$, SE = 35.2, $p = 0.14$).

Craving

Craving was extremely low; that is, 72% of patients scored 5 (seldom craving) or lower at preassessment. The Wilcoxon signed rank test showed that craving reduced from preassessment ($M = 4.08$, SE = 0.48) to postassessment ($M = 3.39$, SE = 0.41, $z = -3.194$, $p < 0.01$). The Kruskal–Wallis tests on difference scores showed no differences between the groups ($p > 0.20$).

Relapse After 1 Year

Follow-up data were obtained from 61.4% of the patients. The chi-square analysis without predictors was not significant (Table 2). There was also no main effect of ABM (CC: $\chi^2(1) = 0.35$, $p = 0.55$, $\varphi = 0.08$, MI: $\chi^2(1) = 0.29$, $p = 0.59$, $\varphi = 0.06$) or tDCS (CC: $\chi^2(1) = 1.42$, $p = 0.23$, $\varphi = 0.17$, MI: $\chi^2(1) = 0.38$, $p = 0.24$, $\varphi = 0.13$). However, there was the least amount of relapse in patients from the groups that received active tDCS (group 2: 21%, group 4: 31%), compared to sham tDCS (group 1: 38% and group 3: 45%; Table 2). The logistic regression also did not yield any significant effects (step 2, CC: $\chi^2(3) = 2.53$, $p = 0.47$, MI: $\chi^2(3) = 2.10$, $p = 0.55$). There were no significant predictors of relapse and no main effects of tDCS and ABM (Table 3).

DISCUSSION

In this experiment, we investigated the potential beneficial effects of anodal tDCS over the DLPFC, while performing an alcohol ABM training, by studying the effects on craving, alcohol bias, and relapse. We found some evidence of enhanced learning during the training with tDCS; there was a stronger avoidance bias during training in the combined group. However, from pre- to postassessment, no beneficial effects of tDCS on changing attentional bias were found on the attentional bias and the implicit association scores. There were also no effects of tDCS and ABM on relapse.
The only potentially relevant effect in the reaction time data was the difference during training in bias scores while receiving active ABM and tDCS. This fits the expectation that tDCS could enhance bias acquisition (Clarke et al., 2014a). This could be due to a modulation of attentional deployment or due to a more general learning effect. Those receiving tDCS may have been better at noticing and learning the stimulus–response contingency and therefore were able to speed reaction times to probes at the contingent location. However, the lack of effects on the postassessment bias raises the question whether the potential tDCS effects could still be maintained offline. More crucially, the absence of effects in the postassessment bias task could also be due to the difficulties in measuring attentional bias; the visual dot-probe task is very unreliable. One can question the relevance of this finding given the low reliability of the task. However, tasks that give suboptimal correlation effect may still produce robust experimental effects (Hedge et al., 2018). The minor observed effect during training may have been due to the vast amount of trials; all sessions combined the training consisted of 1,872 trials, compared to 120 trials in the assessment. This may cause a small effect to become measurable in an unreliable task. Reaction times were relatively fast and accuracy was high so it was not a necessity to use the stimulus information. Patients were not explicitly told of the training goal; hence, there was no explicit motivation to focus attention on the nonalcoholic pictures. It is unlikely that patients were completely ignoring the contents of the stimuli, due to the inclusion of surprise trials; however, the content of the stimuli appears to have had little impact on their attention. This is congruent with others who have also recently stated that the visual dot-probe task has serious limitations (van Bockstaele et al., 2016). There is a need to develop better paradigms for measuring attentional bias, for example, by including eye tracking or EEG (Kappenman et al., 2014).

We also did not find any tDCS or ABM effect on automatic approach associations toward alcohol with a (more reliable) implicit association test. This specific sample of patients already demonstrated a very negative attitude toward alcohol and already showed an indication of alcohol avoidance association before the intervention. In previous studies, approach associations were found at baseline (Eberl et al., 2013; Wiers et al., 2013) but not in Rinck and colleagues (in press). This could be the result of random variation (approach and avoidance biases both occur) or simply a lack of power (the other studies were larger). Nevertheless, in the absence of a specific detrimental bias, it is difficult to determine which automatic processes could be targeted with CBM. There was no effect of tDCS on craving, which was not entirely surprising, given that craving was very low, as shown in the previous studies in a clinical inpatient context (Schoenmakers et al., 2010; Wiers et al., 2011). Future studies could use more active craving manipulations than simple pictures of alcohol stimuli, for example, videos, or more context relevant pictures or situations (instead of the safe environment of the clinic). Another useful addition could be to include craving induction with imagery or stress manipulations (Sinha, 2007). In the current study, patients were already abstinent, and a previous study also found an effect of CBM during detoxification (Manning et al., 2016). It may be more useful to do an intervention while patients feel stronger automatic or subjective approach tendencies toward the alcohol.

tDCS was not found to influence automatic biases or craving, and no effect on relapse was found. However, the effects were going in the expected direction with 16% less relapse in active tDCS groups, which was of comparable magnitude to the effect found in the previous study (den Uyl et al., 2017) that showed a trend-level effect with 19% less relapse. The absence of significant effects in the current study could be due to a large amount of dropout in the follow-up. With other studies in mind (Boggio et al., 2008; Klauss et al., 2014), it is still possible that tDCS over the DLPFC can have a beneficial effect on addiction treatment, although more research is necessary to increase understanding of underlying neurocognitive mechanisms. If not due to an effect on automatic processes, stimulating the DLPFC repeatedly may, for example, have led to a general increase in neuroplasticity and better retention during the cognitive behavior therapies (Stagg and Nitsche, 2011). The most appropriate electrode montage is also a topic of debate, as different protocols have been used. Perhaps more optimal results could be obtained with right anodal DLPFC stimulation, differently sized electrodes, or different stimulation lengths (Jansen et al., 2013; Klauss et al., 2014).

Except for a minor effect during training, this study did not yield evidence that anodal tDCS over the DLPFC could enhance the effectiveness of alcohol ABM training in alcohol treatment. ABM training did not have any effects on bias or other clinical measures, which is likely due to problems in measuring the underlying bias and a low sample, as a larger recent study did find the effect on the attentional bias (Rinck et al., in press). tDCS also did not affect craving or relapse, which might be due to low reporting of craving and high dropout at follow-up. As in previous studies, the dot-probe
task showed very low reliability (Ataya et al., 2012; van Bockstaele et al., 2016; Kappenman et al., 2014). Care should be taken that psychometric properties of tasks are reported and that more valid and more reliable clinical outcome measurements are used. This study does not demonstrate any benefit in the specific combination of tDCS and CBM; however, it does not exclude the potential use of tDCS and CBM. Given the amount of review articles CBM and tDCS inspired in the last years, these techniques are a hot topic of debate (e.g., Antal et al., 2015; Cristea et al., 2016; Horvath et al., 2014; Wiers, 2018; Wiers et al., 2018). The field of research would benefit from large experimental trials to provide further answers. Underlying mechanisms of ABM should be further explored to find potential targets for enhancement. In addition, tDCS is a feasible technique with little side effects that may be useful as an add-on to treatment, but a more appropriate method of tDCS application should be further investigated.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1.** Supplementary materials on side-effects, blinding, mood, and working memory.

**Fig. A.** Overview of reported side-effects.

**Fig. B.** Stimulation type blinding.

**Fig. C.** Pre and post scores for working memory and mood.