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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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Abstract

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 four groups in a two-by-two factorial design. Patients received four sessions of ABM (control or real training) combined with 2mA tDCS (active: 20 min or sham: 30 sec) over the left DLPFC. 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 ($p<.05$). From pre- to post-assessment, there were no main or interaction effects of tDCS and ABM on the bias scores, craving, or relapse ($p>.2$). Although, 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 outcomes measurements (e.g. lack of craving, high drop-out, and unreliable measurements) or aspects of the intervention, should be further investigated.

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1. Introduction

For someone with an alcohol use disorder (AUD) the image of alcohol can be a salient stimulus that captures attention and activates an emotional response (Franken, 2003). Automatically triggered responses to alcohol are potentially relevant for various stages of AUD and have been studied broadly (for a review, see: Wiers et al., 2013). Cognitive bias modification (CBM) paradigms are a family of novel interventions that aim to directly address these processes. In these paradigms, relatively automatic responses are retrained into more beneficial reactions with computerized training. Several CBM studies (mostly with another variety of CBM: approach bias retraining) have shown positive findings in alcohol-dependent populations (Eberl et al.,2013; Manning et al., 2016; Rinck et al., in press; Schoenmakers et al., 2010; Wiers et al., 2011). The current clinical study focused on attentional bias modification (ABM), in which participants are trained to no longer focus attention on alcohol-related stimuli.

An attentional bias is often measured with a Visual Probe Task (VPT) in which targets can follow non-alcohol or alcohol-related stimuli. A relatively fast response time when a target is presented on the location where the alcohol-related stimuli had been indicates an attentional bias. In a training version, targets usually appear at the location of non-alcohol stimuli, training attention away from the alcohol. Most ABM studies included smokers or hazardous drinkers; as of yet only three ABM studies have been published with an alcohol dependent sample (see for review: Wiers, Boffo & Wiers, 2018). At the start of the current study a first small study ABM was found to reduce attentional bias and time to relapse (Schoenmakers et al., 2010). In a second small study, AUD patients with high levels of comorbid social anxiety performed ABM both for alcohol and for social anxiety; no effects were found (Clerkin et al., 2016). A recent large study (N>1400) examined the effects of ABM (real/sham) and a different form of CBM (approach bias modification) and found

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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, Kok, & Cuijpers, 2016; Macleod, 2012; Wiers, Boffo, & Field, 2018), also with regards to anxiety research, a field where ABM has been tested more extensively (Beard, 2011; Emmelkamp, 2012; Clarke, Notebaert, Macleod, 2014; Cristea, Kok, & Cuijpers, 2015; Mogoase, David, Koster, 2014). Regarding anxiety, Macleod & 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 of bias. It is therefore relevant to further investigate ABM in a clinical sample, and examine if 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 RCTs and "cast serious doubts on the clinical utility of CBM interventions for addiction problems" (Cristea et al., 2016). 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 effects of ABM could be augmented by stimulating relevant neural networks.

An attentional bias towards 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 & Berridge, 1993). From an evolutionary perspective, it makes sense that rewarding stimuli rapidly grab

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attention (Theeuwes & Belopolsky, 2012; Chelazzi et al., 2013). 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, Munafo, Franken, 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, like 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 & Rubia, 2012; Bishop, 2009; Browning et al., 2010).

Clarke et al. (2014) 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 & Paulus, 2000; Rahman et al., 2013), increase cognitive performance (Hill, Fitzgerald, & Hoy, 2015; Nitsche & Paulus, 2011), and enhance effects of cognitive training (Elmasry, Loo, & Martin, 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

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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 approach bias retraining also showed a trend level effect on relapse, although it did not lead to a stronger bias at post-test (den Uyl et al., 2017). Modulating approach bias with tDCS in a heavy drinking population was also not successful (den Uyl, Gladwin, & Wiers, 2015). In this study we want to investigate whether tDCS can have an effect on attentional bias modification training and craving in a clinical setting with alcohol dependent inpatients.

We tested whether four sessions of ABM (control vs. real) training combined with 2 mA anodal DLPFC tDCS (sham vs. active) had beneficial effects on behaviour 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 et al., 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.

2. Materials and Methods

2.1. Participants

Inpatients were recruited from the Salus Clinic in Lindow, Germany, where inpatient treatment takes an average of three months. Patients were included into 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,

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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 (Figure 1), thirteen dropped out during testing (ten no reason/no further motivation, one due to craving, one due to relapse, one due to an inclusion error), two were later excluded (one was analphabetic, one 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).

2.2. Design and Intervention

2.2.1. Design: We used a 2x2 double blind factorial design (control vs. real ABM and sham vs. active tDCS). Patients were randomly assigned to one of the four experimental groups. The tDCS device (NeuroConn DC-stimulator Plus) had a function incorporated that could apply sham or active stimulation with pre-determined codes. In the script for the ABM training a function was also incorporated to determine control or real ABM with pre-determined codes. The codes that determined the placebo or real training variety for each group were covertly randomised within an excel list with the rand function. The training consisted of four sessions of ABM training (control or real) during which patients received either sham or active tDCS.

2.2.2. 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. The 35 cm^2 anodal electrode was positioned over the F3 (10-20 EEG) location

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(used for left DLPFC) and the 100 cm^2 cathodal electrode was positioned over the F4. A 100 cm^2 cathodal electrode was used to approximate unilateral stimulation (Boggio et al., 2009; den Uyl et al., 2017). In order to reduce shunting, we aimed for a 8 cm gab 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, was used.

2.2.3. Attentional Bias Modification: In this task participants were required to respond to probes (arrows pointing up or down), which appeared on the location of one of the preceding pictorial stimuli. The trial started with a fixation cross (with a variable ISI between 500-1000 ms), followed by two pictures on the left and right of the screen presented for 500 ms. These two pictures were followed by an arrow on one of the two locations. For upward arrows, participants were required to press the G of the keyboard, for downward arrows the B, the probe remained on the screen until a response was given. The attentional bias task was made similar to Zvielli et al., (2014) and also included trials on which the target was absent and surprise trials. The two stimuli were either alcohol and non-alcohol beverages, or in some cases two non-alcohol beverages (absent target), or two objects (surprise trial). In the training version the probe appeared after the non-alcohol stimulus in 9 out of 12 trials, and the probe appeared after the alcohol stimulus in 1 out of 12 trials (contingency probe after non-alcohol vs. probe after alcohol: 90-10%); in the control version of the training the contingency was kept equivalent (5/12 probe after alcohol, 5/12 probe after non-alcohol). In 1 out of 12 trials, the two stimuli were both non-alcohol, and in another 1 out of 12 of the trials the two stimuli were both objects. The trials with objects were surprise trials, to increase semantic processing of the pictures, and required a different response (pressing the space bar; Zvielli et al., 2014). For the trials with alcohol and non-alcohol stimuli, 16 alcohol and 16 non-alcohol stimuli

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were used, 16 different non-alcohol images were used for the absent target trials. The pictures were matched on colour (e.g. vodka with water), and composition (e.g. presence of a glass/person). Local beverages were used and the images were shot according to the protocol from Pronk et al. (2015). Each training session consisted of 468 trials, which took approximately 15 to 20 minutes (depending on the reaction time of the participant). When the training was completed before the 20 minutes of tDCS, the participant remained seated until the stimulation time was also finished.

2.3. Outcome Measures

2.3.1. Alcohol Visual Probe Task: The design of the VPT was similar to the ABM training, only with equal amounts of alcohol, non-alcohol, and absent target trials (36 trials each), it included 12 surprise trials. The first session was preceded by 20 practise trials to familiarize participants with the task. We calculated the original attentional bias score by subtracting average reaction times (only for accurate trials, and outliers >3 SD were deleted) for the congruent (alcohol target) trials from the incongruent (non-alcohol target) trials. Reliability scores were calculated by taking the split-half (first half vs. second half) and the test-retest (pre-assessment vs. post-assessment) correlations.

2.3.2. Implicit Association Task: Transfer in approach and avoidance associations was measured with a seven block IAT (Ostafin & Palfai, 2006). Words were presented in the centre of the screen and were categorised 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 non-alcohol (e.g. cola), and attribute categories were approach (e.g. grab) or avoid (e.g. push away). Each attribute categories were shown together in one block to measure the speed to categorise alcohol with approach (and non-alcohol with avoid) and vice versa. The blocks

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were organised into target category practise (block 1, 24 trials), attribute category practise (block 2, 24 trials), combined approach-alcohol (practise block 3, 24 trials, test block 4, 48 trials), reversed target category practise (block 4, 24 trials), combined avoid-alcohol (practise 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. Since order effects can be asymmetrical, all subjects received the same order to increase predictive validity (Perugini, Richetin, & Zogmaister, 2010).

2.3.3. 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 frequency of craving in the previous week.

2.3.5. 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 three different 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 one for relapse without improvement. In our analyses we used a binary scoring with improvement and abstinence together as success, equivalent to previous research (den Uyl et al., 2017).

2.4. Questionnaires

2.4.1. Alcohol Use Disorder Identification Test (AUDIT): The 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.

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

2.4.3. Symptom Checklist 90-R (SCL90-R): The 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, GSI) as a general indication.

2.4.4. Adverse Effects tDCS Questionnaire: Side-effects of the stimulation were assessed with a questionnaire that checked 10 possible side-effects (itching, tingling, burning, scalp pain, neck pain, headache, dizziness, sleepiness, trouble concentrating, nausea). Answers could be given from 0 (not present), to 3 (strongly present). We also included two questions on the estimated strength and the uncomfortableness of the stimulation, on a scale of 1 to 10.

2.5. 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 appointments to participate in the study. During the first appointment patients were randomly assigned to one of the four groups and gave written informed consent. During the pre- or post-assessment 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[1]. The first training session was started directly after the pre-

[1] We included multiple craving measurements (alcohol urge questionnaire (AUQ), and Visual Analogue Scales), which assessed momentary craving, however, due to low scores it did not give additional information and was

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assessment. The four training sessions were done within one week. The post-assessment was done at least one day and maximum seven days after the last training session (with one exception, due to illness one patient had the post-assessment ten days after the last training session).

2.6. Data Analysis

Baseline group differences on demographics and questionnaires (AUDIT, SCL90-R, BDI) are entered in a MANOVA and ANOVA comparisons for each variable with group as between subject variable are reported. The PACS scores were analysed with non-parametric tests. An effect of time was investigated with the Wilcoxon signed rank test and Kruskal Wallis test were used on difference scores for group effects. The continuous data (attentional bias, and approach associations) were analysed with a repeated measures ANOVA with time as within-subjects factor, the group variables ABM (control vs. real) and tDCS (sham vs. active) were entered as between-factors. For each variable in the continuous data, participants with scores higher than three times the standard deviation were considered outliers and were adjusted to the highest score + 1 (no more than three participants were adjusted for each variable). For the analysis on relapse we performed a logistic regression with complete cases and multiple imputation (MI) analysis. We used all demographic variables from Table 1 and the outcome measures from Table 2 as predictors. We performed 40 imputations (since we had 40% missing data, Bodner, 2008) with SPSS 20. In step 1 of the regression we used the same predictors as similar studies (den Uyl et al., 2017). In step 2 we entered the group variables ABM (coded as -1, 1), tDCS (coded as -1,1), and the interaction (ABM x tDCS) as dummy

excluded from the paper. We assessed Visual Analogue Scales on Mood at the beginning and end of experimental sessions. Brief results on the Working Memory task and mood questionnaires are included in the supplementary materials. Analysis on physiological findings will be reported elsewhere.

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variables. 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).

3. Results

All patients tolerated the stimulation well, and there were no differences in reported side-effects between sham and active stimulation (see Supplementary Materials). There was no difference in how often people thought they had received real stimulation whether they were in sham or active tDCS group ($\chi 2(4)=4.5$, p=.35). There were no significant differences between any of the baseline variables (Table 1).

3.1. Attentional Bias

The attentional bias score showed poor split-half correlations (r=-.07); and a poor test-retest correlation (r=.15). The bias score at baseline did not correlate with alcohol problems (r=-.04) or craving (r=-.06). The accuracy on the ABM task in the pre-assessment was very high (Mean: 96.7%, SD = 3.7); except for two 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 post-assessment) and experimental group (control/real ABM and sham/active tDCS) there were no significant interactions (p>.46, Table 2). There was a main effect of Time ($F(1,77)=4.03$, p=.048, $\eta^2=.05$), the overall bias went from a slight avoidance (one-sample t-test: M= -8.03, p=.06) to more neutral at post-assessment (M=0.54, p=.59).

We also analysed the attentional bias during training. An ANOVA with Time (4 sessions) was run for the different attentional bias scores (due to infrequent alcohol-target

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trials this could also be done for the real-ABM training). The bias score showed no significant within-subjects main effects or interactions with group ($p>0.15$), however a significant between-subject effect was found for ABM ($F(1,79)=4.87$, $p=.03$, $\eta^2=.06$), and for the interaction between tDCS and ABM ($F(1,79)=4.17$, $p=.04$, $\eta^2=.05$). 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 non-alcohol target), for those in the group that received both real ABM and active tDCS compared to the other groups (group 4 vs. group 1 $p=.046$, vs. group 2 $p=.02$, vs. group 3 $p=.08$; Figure 2).

3.2. Implicit Alcohol Approach Association

The IAT approach association score showed good split-half correlations ($r=.83$); and good test-retest correlations ($r=.72$). The baseline score did not correlate with alcohol problems ($r=-.09$) or craving ($r=.14$). An ANOVA on the bias scores with Time (pre-assessment and post-assessment), tDCS, and ABM did not give any significant main or interaction effects ($p>.44$, Table 2). The overall bias was slightly negative at baseline, in the direction of an avoidance association, but this was not significant ($M=-52.5$, $SE=35.2$, $p=.14$).

3.3. Craving

Craving was extremely low, 72% of patients scored 5 (seldom craving) or lower at pre-assessment. Wilcoxon signed rank test showed that craving reduced from pre- ($M = 4.08$, $SE=0.48$) to post-assessment ($M=3.39$, $SE=.41$, $z =-3.194$, $p<0.01$). Kruskal Wallis tests on difference scores showed no differences between the groups ($p>.20$).

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3.4. Relapse after one year

Follow-up data was 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: $\chi2(1)=.35$. $p=.55$, $\varphi=.08$, MI: $\chi2(1)=.29$, $p=.59$, $\varphi=.06$) or tDCS (CC: $\chi2(1)=1.42$. $p=.23$, $\varphi=.17$, MI: $\chi2(1)=.38$. $p=.24$, $\varphi=.13$). Although, 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%, group 3: 45%, see Table 2). The logistic regression also did not yield any significant effects (step 2, CC: $\chi2(3)=2.53$, $p=.47$, MI: $\chi2(3)=2.10$, $p=.55$). There were no significant predictors of relapse and no main effects of tDCS and ABM (Table 3).

4. Discussion

In this experiment we investigated the potential beneficial effects of anodal tDCS over the DLPFC, while performing an alcohol attentional bias modification (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 post-assessment, 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., 2014). 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

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therefore were able to speed reaction times to probes at the contingent location. However, the lack of effects on the post-assessment bias, raises the question whether the potential tDCS effects could still be maintained offline. More crucially, absence of effects in the post-assessment bias task could also be due to 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 correlational effect, may still produce robust experimental effects (Hedge et al., 2017). The minor observed effect during training may have been due to the vast amount of trials; all sessions combined the training consisted of 1872 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 non-alcoholic 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 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 towards alcohol with a (more reliable) implicit association test. This specific sample of patients already demonstrated a very negative attitude towards 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., 2011; Wiers et al., 2013), but not in Rinck et al., 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

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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 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, 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 towards 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 found a trend level effect with 19% less relapse. Absence of significant effects in the current study could be due to large amount of drop-out 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 behaviour therapies (Stagg & Nitsche, 2011). The most appropriate electrode montage is also topic for debate, since different protocols have been used. Perhaps more optimal results could be obtained with right anodal DLPFC stimulation,

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differently sized electrodes, or different stimulation lengths (Janssen 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 attentional bias modification 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 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 drop-out at follow-up. As in previous studies the dot probe task showed very low reliability (Ataya et al., 2012; Kappenman et al., 2014; van Bockstaele et al., 2016). 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. Christea et al., 2016; 2018; Wiers et al, 2018; Horvath et al., 2014; Antal et al., 2015). 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 it 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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Figure 1. Flow Diagram according to CONSORT 2010. Intervention 1 consists of control-ABM combined with sham-tDCS, intervention 2: control-ABM combined with active tDCS, intervention 3: real-ABM combined with sham-tDCS, intervention 4: real-ABM combined with active-tDCS.

Figure 2. Bias scores during training. Since there is only a significant interaction of ABM x tDCS (without an interaction with Time), average bias scores over all four training sessions are given per group. Error bars represent standard error of the mean. Group 4 that received real-ABM and active tDCS differs significantly from group 1 and 2; there is a trend level difference with group 3 ($p=.08$).

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	1. control-ABM + sham-tDCS		2.control-ABM + active tDCS		3. real-ABM + sham-tDCS		4. real-ABM + active-tDCS		Total		
	M	SE	M	SE	M	SE	M	SE	M	SE	p
Gender (F/M)	5/17		4/16		5/15		7/14		21/62		.779
Smoker (Y/N)	13/9		16/4		17/3		14/7		60/23		.217
Age (years)	48.23	1.93	48.65	1.63	49.20	1.98	48.38	2.06	48.60	0.94	0.99
Duration of alcohol problems (years)	18.15	2.28	15.37	2.31	16.80	2.89	19.00	2.44	17.37	1.23	0.75
Alcohol problems (AUDIT score)	27.27	1.66	23.70	1.52	24.40	1.47	26.00	1.50	25.40	0.77	0.36
Number of detoxifications	4.00	1.29	1.80	0.77	2.80	0.79	3.71	1.12	3.11	0.52	0.43
Duration of treatment (days)	80.59	2.53	80.30	3.78	75.10	4.30	73.43	3.70	77.39	1.80	0.38
Start experiment (days)	10.68	1.05	11.30	1.22	10.00	1.11	12.62	1.49	11.16	0.61	0.49
Depression (BDI score)	14.27	2.67	12.57	2.41	11.10	2.96	12.52	2.33	12.66	1.28	0.86
Mental burden (GSI SCL-90 score)	58.18	3.44	58.27	3.05	57.40	3.20	58.33	3.21	58.05	1.59	1.00
Craving baseline (PACS score)	3.59	0.68	2.95	0.64	5.45	1.26	4.38	1.08	4.08	0.48	0.30

Table 1. Demographic variables. Overview of the mean (M) and standard deviation (SD) of the baseline scores for all demographic variables per group. AUDIT=Alcohol use Disorder Identification Test, BDI=Beck's Depression Index, SCL-90=Symptom Checklist-90—Revised, PACS=Pennsylvania Alcohol Craving Questionnaire. The p-values represents outcomes of an ANOVA with group as between subject variable.

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a.		1. control-ABM + sham tDCS		2. control-ABM + active tDCS		3. real-ABM + sham tDCS		4. real-ABM + active tDCS		
Outcome measurements		M	SE	M	SE	M	SE	M	SE	*p*
Craving (PACS)	Pre-assessment	3.6	0.9	3.0	1.0	5.5	1.0	4.4	0.9	.20
	Post-assessment	3.3	0.8	2.7	0.8	4.0	0.8	3.6	0.8	
Attentional Bias	Pre-assessment	-2.1	6.9	-6.2	6.2	-14.3	6.6	-5.7	11.1	.46
	Post-assessment	3.5	5.9	3.0	6.9	2.7	7.2	0.6	6.0	
IAT	Pre-assessment	-71.6	79.4	-91.8	83.2	18.9	55.5	-62.9	61.3	.63
	Post-assessment	-58.7	67.5	-68.3	60.7	10.3	60.7	-11.6	75.7	

b.										
Outcome measurements		relapse	success	relapse	success	relapse	success	relapse	success	
Relapse after one year		9.0(5)	13.0(8)	5.7(3)	14.3(11)	9.1(5)	10.9(6)	6.8(4)	14.2(9)	.56(.61)

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 post-assessment, p-values represent outcomes of the ANOVA interaction time x ABM x tDCS (or non-parametric test on difference score for PACS). PACS = Pennsylvania Alcohol Craving Questionnaire. (b.) For relapse rates the Multiple Imputation estimates are given with complete case results between brackets. The p-values represent outcomes of a chi-square test.

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		1 year relapse		
	Variable	*B*	*S.E.*	*p*
Step 1	Gender	.110	.755	.885
	Duration alcohol problems	-.026	.032	.429
	Number of detoxifications	.020	.066	.765
	Alcohol problems (AUDIT)	.030	.048	.537
	Duration of treatment (days)	-.008	.018	.673
	Depression (BDI)	.020	.039	.610
	SCL-90-R	-.009	.033	.777
Step 2	ABM	.114	.297	.701
	tDCS	-.286	.297	.336
	ABM x tDCS	-.035	.303	.907

Table 3. Logistic regression results with multiple imputation data for 1 year relapse data. AUDIT = Alcohol use Disorder Identification Test, BDI = Beck's Depression Inventory, SCL-90 =Symptom Checklist-90-Revised, PACS = Pennsylvania Alcohol Craving Questionnaire.

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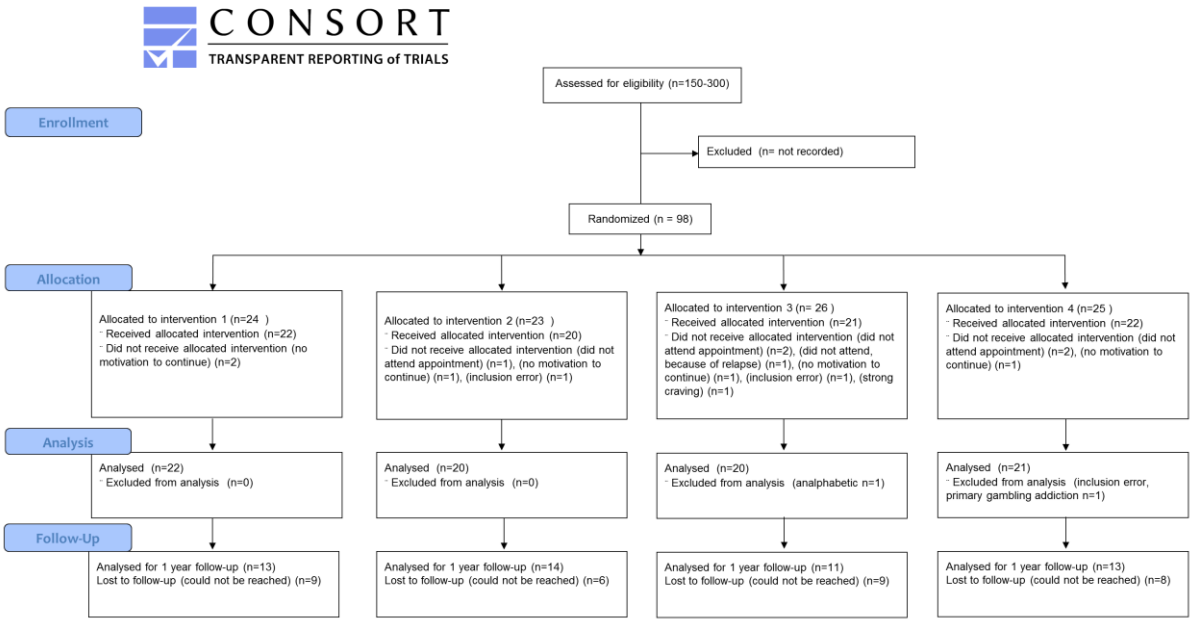

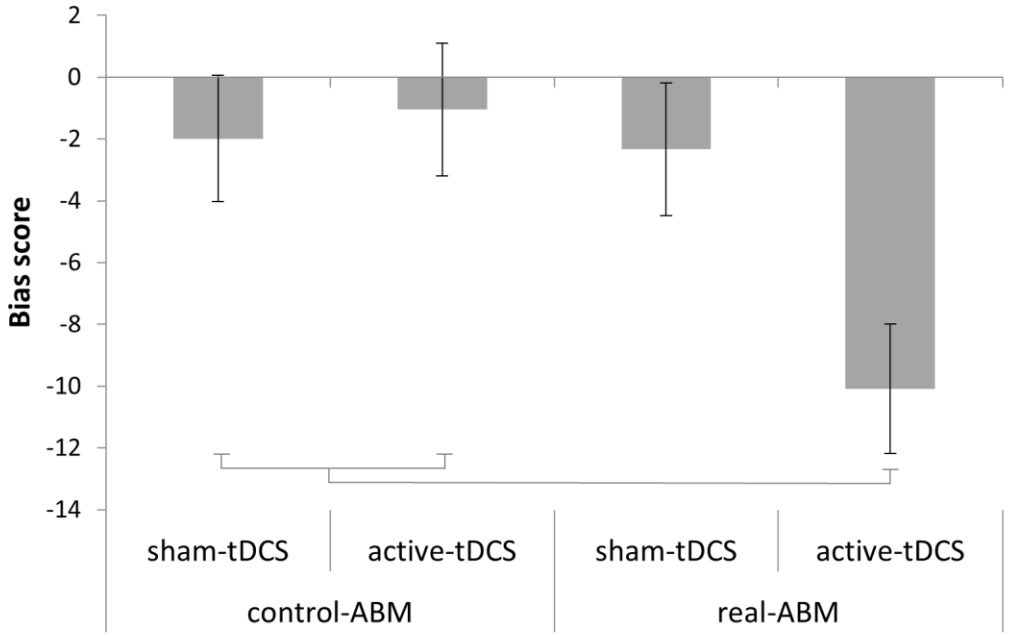

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