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Relapse Prevention in Abstinent Alcoholics by Cognitive Bias Modification: Clinical Effects of Combining Approach Bias Modification and Attention Bias Modification

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Objective: Alcohol-dependent patients show attentional and approach biases for alcohol-related stimuli. Computerized cognitive bias modification (CBM) programs aim to retrain these biases and reduce relapse rates as add-ons to treatment. Retraining of alcohol-approach tendencies has already yielded significant reductions of relapse rates in previous studies, and retraining of biased attention toward alcohol is promising approach. The current large-scale randomized controlled trial compared the clinical effects of these training methods—separately and in combination—to those of sham training methods and a no-training control, as an add-on to regular treatment. ***Methods:*** Participants were 1,405 alcohol-dependent patients of an inpatient rehabilitation clinic. In addition to regular treatment, patients were randomized to receive 6 sessions of approach-bias retraining, 6 sessions of attention-bias retraining, 3 sessions of each of these CBM training varieties, 6 sessions of variants of sham training, or no training. Effects of the training methods were evaluated by measuring treatment success at 1-year follow-up. ***Results:*** Primary outcome: The 3 active training conditions yielded higher success rates at 1-year follow-up than sham training or no training (8.4%, on average). Secondary results (available for half of the sample): Both varieties of CBM had only small effects on the targeted biases (significant only for the combined training). Moreover, neither significant mediation of the clinical effect by the change in trained bias nor significant moderation of the clinical effect was found. ***Conclusions:*** Both alcohol-avoidance training and alcohol-attention training increased success rates effectively, as did the combination of both methods. Future studies should test ways to increase training effectiveness further.

What is the public health significance of this article?
This large-scale study shows that relapse rates in abstinent alcohol-dependent patients can be reduced both by training to avoid alcohol pictures and by training to direct attention away from them. This offers new and cost-effective add-on treatments for alcohol addiction.

Keywords: cognitive bias modification, alcohol-attention bias, alcohol-approach bias, alcohol dependence, relapse prevention

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Why do so many people suffering from an addiction relapse, even when they are highly motivated to change their self-destructive behaviors? This apparent paradox can be explained at least partly by translational etiological models that assume that all behaviors, including addictive behaviors, can be triggered automatically (Stacy & Wiers, 2010; Strack & Deutsch, 2004). According to these models, addictive behaviors are characterized by an imbalance between these strong impulsive cue-induced reactions to drug-related stimuli, on one hand, and relatively weak control over these impulses, on the other hand (Bechara, 2005; R. W. Wiers et al., 2007). The current article focuses on the manipulation of two of these biased cognitive processes in alcohol addiction: the attentional bias (AtB) for alcohol-related stimuli and the biased action tendency to approach alcohol-related stimuli (approach bias, ApB).

Both heavy drinkers and alcohol-addicted individuals have been shown to have an AtB toward alcohol-related stimuli, which has

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been found to predict consumption levels and the likelihood of relapse (Christiansen, Schoenmakers, & Field, 2015; Field & Cox, 2008). Regarding biased action tendencies, heavy drinkers and alcohol-dependent patients, when compared to controls, show a tendency to approach alcohol-related stimuli (R. W. Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011; R. W. Wiers, Rinck, Dictus, & van den Wildenberg, 2009; review: Kakoschke, Kemps, & Tiggemann, 2017).

Cognitive models postulate that these biased cognitive processes contribute to the maintenance of mental disorders, including addictions (Williams, Watts, MacLeod, & Mathews, 1997). Therefore, a new class of translational interventions was developed, collectively called cognitive bias modification (CBM, review: R. W. Wiers, Gladwin, Hofmann, Salemink, & Ridderinkhof, 2013). The initial goal of CBM was to test the postulated causal role of the biases, typically tested in two directions—increase or decrease the bias—in nonclinical student samples (e.g., Field & Eastwood, 2005; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; R. W. Wiers, Rinck, Kordts, Houben, & Strack, 2010). Second, randomized controlled trials (RCTs) were conducted in clinical samples to test whether maladaptive cognitive biases could be reduced and whether that would result in improved treatment outcomes (see R. W. Wiers et al., 2013).

CBM in addiction started with proof-of-principle studies in students on AtB modification (Field et al., 2007; Field & Eastwood, 2005; Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007), modeled after the seminal work in anxiety by MacLeod et al. (2002). Results showed that it was indeed possible to change the alcohol AtB, but the effect did not generalize to untrained pictures or to other outcomes such as craving or drinking in a taste test (Field et al., 2007; Schoenmakers et al., 2007). One small first RCT was performed in patients who received five sessions of AtB modification on top of regular treatment, with promising results: generalized reduction of AtB (also to untrained pictures), earlier treatment discharge, and later relapse (Schoenmakers et al., 2010). However, later studies in clinical samples using varieties of AtB modification procedures reported mixed results (Clerkin, Magee, Wells, Beard, & Barnett, 2016; Cox, Fadardi, Hosier, & Pothos, 2015; R. W. Wiers et al., 2015; review: R. W. Wiers, Boffo, & Field, in press).

Regarding RCTs on ApB modification, after promising results in a proof-of-principle study in students (R. W. Wiers et al., 2010), a first RCT was conducted, which found that alcohol-dependent patients who received four sessions of ApB modification in addition to regular treatment showed less relapse 1 year after treatment discharge, compared with patients who received no training or sham training (R. W. Wiers et al., 2011). This effect was replicated in a second large study (Eberl et al., 2013), which also revealed mediation of the clinical effect by the change in alcohol-approach bias. Moreover, this mediator was moderated by the strength of the approach bias at pretest (those with a stronger bias changed more). In addition, the clinical effect was moderated by the patients' age. A recent neurocognitive study demonstrated that ApB modification reduced amygdala cue-reactivity more strongly than sham training (C. E. Wiers et al., 2015), and a recent study found promising effects of training during detox (Manning et al., 2016). In sum, ApB modification has shown consistent promising effects in clinical contexts (for reviews, see Kakoschke et al., 2017; R. W. Wiers et al., in press), and therefore, it was recently added to the German guidelines for the treatment of alcohol dependency (Mann et al., 2016). Note that a recent meta-analysis on CBM in addiction claimed to cast "serious doubts on the clinical utility of CBM interventions for addiction" (Cristea, Kok, & Cuijpers, 2016). However, this meta-analysis combined different substances (smoking, alcohol), training methods, and, most important, proof-of-principle studies in students not motivated to change with RCTs in clinical samples (see R. W. Wiers et al., in press).

Based on these findings, the current study tested the separate and combined effects of AtB and ApB modification, in a large-scale RCT, comparing both CBM training varieties and their combination to corresponding sham training controls and a no-training control. For ApB modification, we used the same joystick-training task as in the studies reported by R. W. Wiers et al. (2011) and Eberl et al. (2013), a modification of the Alcohol-Approach-Avoidance Task (Alcohol-AAT), in which patients in the active condition were trained to push away (avoid) alcohol pictures. For AtB modification, a joystick variant of the so-called dot-probe task (DPT) employed previously (e.g., Schoenmakers et al., 2010) was used (the Alcohol-DPT), in which patients were trained to orient their attention away from alcohol. Patients received six sessions of training (AAT/DPT based) or sham training (continued assessment). In order to control for the number of training sessions (which affects outcome; Eberl et al., 2014), the combined-training group received three sessions of AAT training and three of DPT training. Primary outcome variable was the clinical outcome: status at 1-year follow-up (relapse or not, as in Eberl et al., 2013; R. W. Wiers et al., 2011).

Method

Participants

Participants were 1,405 currently abstinent alcohol-dependent patients administered to a 3-month inpatient treatment in the salus clinic Lindow in Germany. Previous research has repeatedly shown a small effect of the AAT training involving approximately a 10% reduction of relapse rates (Eberl et al., 2013; R. W. Wiers et al., 2011). Therefore, the current sample size was calculated to yield a power of $1 - \beta = .96$ with $p = .05$ for the detection of a small effect ($w = .10$) in the main comparison of the active training groups versus the control groups. Moreover, each of the five groups described below exceeded the sample size at which at 10% difference in relapse rates would be statistically significant ($N = 200$). Patients were informed about the study and their option to withdraw from it, without incurring any disadvantages regarding their treatment. Included patients signed informed consent and were randomly assigned to one of the experimental groups described below. Every patient had a primary diagnosis of *DSM–IV* alcohol dependence. Exclusion criteria were nonnative speakers of German, neurocognitive problems, strong withdrawal symptoms, history of schizophrenia, and visual or motoric handicaps. Patients with severe neurological disorders such as Korsakoff syndrome are not admitted to the salus clinic. None of the patients received anticraving medication. Figure 1 shows a CONSORT diagram of the participant flow, and the characteristics of the sample are shown in Table 1. The five groups created for the analyses described below did not differ significantly in percentage of dropouts at follow-up, gender distribution, age, education level, severity and

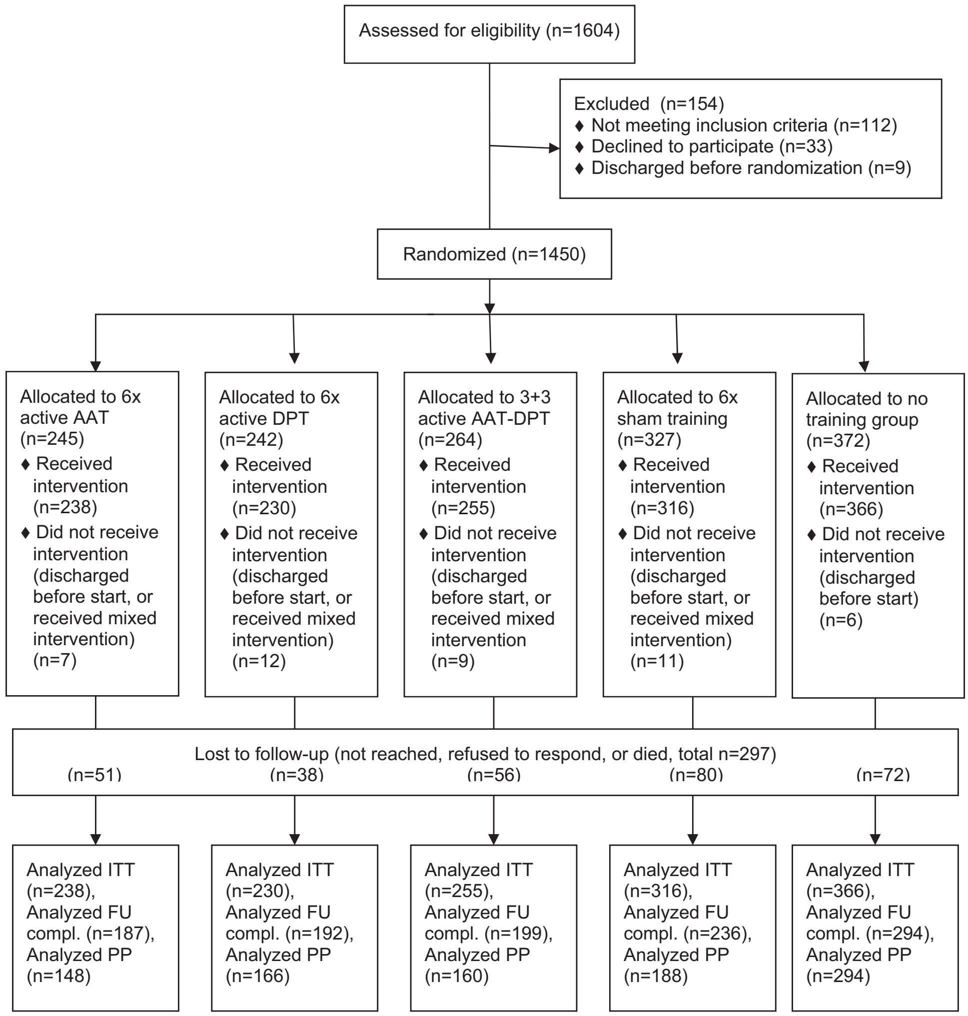

Figure 1. CONSORT diagram. The sample sizes shown here relate to analyses of the primary outcome variable "success at 1-year FU." ITT is the intention-to-treat analysis using DGSS-4 rules (includes all 1,405 correctly randomized patients). "FU complete" analysis is according to DGSS-1 (includes only the 1,108 patients reached at follow-up). "PP" analysis is per protocol (includes only the 956 patients who completed the training and were reached at follow-up).

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duration of alcohol dependence, nicotine dependence, depression, or general mental burden. Moreover, the four groups that received some sort of training did not differ in the mean number of training sessions completed (see Table 1).

Procedure Overview

During the first 2 weeks of treatment, all patients completed a battery of computer tasks, including the Alcohol-AAT pretest and the Alcohol-DPT pretest. Patients who fulfilled the inclusion and exclusion criteria were then randomly assigned to one of the experimental groups described below. Therapists were blind to the assignment, except that they knew which group was the no-training control group. Patients assigned to one of the trained groups were scheduled to complete six sessions of training (15–20 min each) within the next 2 weeks, in addition to treatment as usual. The latter consisted of abstinence-orientated cognitive–behavioral therapy (CBT), including individual and group sessions. After the training sessions and before treatment discharge, all patients were scheduled to participate in the posttest versions of the Alcohol-AAT and the Alcohol-DPT. One year after treatment discharge and as part of the routine clinical procedure, participants received a standard follow-up questionnaire (like all other patients). Importantly, the questionnaire asked whether patients had been continuously abstinent during the past year. If they denied, additional questions addressed the type of drugs consumed, the duration of abstinence after treatment discharge, the duration of the current abstinence (if currently abstinent), the number and duration of the relapse(s), and the way the last relapse was ended (see online supplemental materials). Patients who did not return the questionnaire were reminded by post twice, and finally an attempt was

Table 1
Main Sample Characteristics: Means (SDs), Significance of Group Differences, and Success Rates at 1-Year Follow-Up (Includes Abstinence and Lapse)

Variable	6× AAT training	6× DPT training	3 + 3 training	Sham training	No training	*p* value
N	238	230	255	316	366	
Gender (% male)	71	71	74	73	78	.50
Age, mean (*SD*), y	45.4 (9.2)	45.9 (9.7)	45.3 (8.8)	45.5 (9.7)	46.4 (9.7)	.62
Education level, mean (*SD*)	3.4 (1.0)	3.5 (0.9)	3.5 (1.0)	3.4 (1.0)	3.3 (1.1)	.32
AUDIT score, mean (*SD*)	24.5 (8.7)	25.1 (8.3)	25.9 (8.2)	24.8 (8.9)	24.6 (9.0)	.64
Years of dependence, mean (*SD*)	12.9 (9.4)	12.8 (9.1)	14.5 (9.5)	13.3 (8.7)	14.0 (9.3)	.28
Smoking: Fagerström score, mean (*SD*)	4.5 (3.0)	4.4 (2.5)	4.3 (2.7)	4.2 (2.7)	4.2 (3.0)	.91
Depression: BDI score, mean (*SD*)	14.6 (12.3)	14.1 (12.3)	13.6 (11.1)	13.5 (10.4)	13.1 (12.2)	.84
Mental burden: SCL-90 score, mean (*SD*)	57.0 (15.1)	57.1 (14.7)	57.8 (11.2)	57.9 (12.2)	58.2 (14.6)	.93
Completed training sessions (out of 6), mean (*SD*)	5.0 (2.1)	5.3 (1.9)	5.2 (1.8)	4.9 (2.2)	.0 (.0)	.13[a]
Percent dropouts at follow-up	21	17	22	25	20	.15
Percent success at follow-up (ITT)	52.1	55.2	51.4	43.4	45.4	

Note. AAT = approach-avoidance task; DPT = dot-probe task; AUDIT = Alcohol Use Disorders Identification Test; BDI = Beck Depression Inventory; SCL-90 = Symptom Checklist–90; ITT = intention to treat.
[a] The *p* value refers to comparison of the first four groups only, without the no-training group.

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made to reach them by phone. The patients were contacted by therapists or interns who did not know whether the patient had participated in the study, let alone which training the patient had received. A total of 1,108 (78.9%) patients could be reached by this procedure. The study was approved by the ethics committee of the Department of Human and Social Sciences of the Technical University Chemnitz, Germany, and registered at the German Clinical Trial Register (ID: DRKS00007797).

Assessment and Outcome Measures

At intake, patients were diagnosed using the computerized version of the Composite International Diagnostic Interview (CIDI; Robins et al., 1988), which was complemented by a diagnostic interview based on the "German Manual for Documentation in Addiction Help" published by the German "Hauptstelle für Suchtfragen DHS." Both the CIDI and the interview formed the basis for the final expert ratings on diagnoses, as made by clinical psychologists. German versions of the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993), the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), the Beck Depression Inventory (BDI; Hautzinger, Bailer, Worall, & Keller, 1994), and the Symptom Checklist 90-R (SCL-90–R; Franke & Stacker, 1995) were also administered at intake. Computerized tasks included pretest and posttest assessment versions of the Alcohol-AAT and the Alcohol-DPT. The main outcome variable of this RCT was the 1-year follow-up (FU) which was evaluated using a binary outcome variable (successful outcome or not), following conservative intention-to-treat (ITT) principles. As defined by the DGSS-4 (Deutsche Gesellschaft für Suchtforschung und Suchttherapie) guidelines of the German Addiction Society, successful outcomes consisted of either no relapse at all or a single lapse shorter than 3 days in duration, ended by the patient without further negative consequences and followed by at least 4 weeks of abstinence until FU. Failure was defined as relapse, death, no contact, or refusal to provide information (as in Eberl et al., 2013; R. W. Wiers et al., 2011). The success rates were analyzed using chi-square tests to compare the number of successes and failures in the different training groups to each other. These ITT analyses were complemented by analyses according to the DGSS-1 standard, which involves only patients reached at FU (excluding death, no contact, and refusal) and by per-protocol analyses, including only patients who completed all six training sessions and were reached at follow-up. Finally, we also computed ITT analyses only for those patients for whom complete pretest and posttest data were available.

Questionnaires

AUDIT. The AUDIT (Saunders et al., 1993) is a screening instrument for problematic alcohol consumption. It addresses drinking amount, frequency, and negative consequences with high test–retest reliability ($r = .95$; Dybek et al., 2006).

FTND. The FTND (Heatherton et al., 1991) is a widely used self-report measure that captures the degree of nicotine dependence. Test–retest reliability of the German version is high ($r = .88$; Bleich, Havemann-Reinecke, & Kornhuber, 2002).

BDI. The German version of the BDI (Hautzinger et al., 1994) was used to measure the severity of depressive symptoms. It has high internal consistency (Cronbach's alpha = .80) and test–retest reliability ($r = .92$; Hautzinger et al., 1994).

SCL-90–R. The German version of the SCL-90–R (Franke & Stacker, 1995) contains 90 items to measure the physical and psychological impairment of a person within the past 7 days. A global severity index computed from it indicates the overall level of distress with excellent internal consistency (Cronbach's alpha = .97; Franke & Stacker, 1995).

Experimental Tasks

The experimental tasks consisted of the Alcohol-AAT and the Alcohol-DPT. Three versions of each task were created: an assessment version used at pretest and posttest, an active training version, and a sham training version. The AAT was structurally identical to the one used by R. W. Wiers et al. (2011) and Eberl et al. (2013), with some updated pictures and 6 sessions instead of 4 or 12. The DPT was conceptually similar to the one used by Schoenmakers et al. (2010).

General aspects of the Alcohol-AAT. The Alcohol-AAT measures action tendencies toward alcoholic and nonalcoholic beverages. In this task, single pictures of familiar beverages (here: 10 different alcoholic and nonalcoholic beverages each) are presented. Patients were asked to make each picture disappear as quickly as possible by moving a joystick attached to the table in front of them either toward or away from them. The correct movement depended on the format of the pictures, irrespective of the pictures' contents. All patients had to push the joystick away from themselves in response to landscape-format pictures and pull in response to all portrait-format pictures. For practical reasons, we decided not to counterbalance response direction and picture format. Pushing the joystick went along with a decrease in picture size and pulling it with an increase in size. This zoom effect strengthens the subjective impression of pulling the picture itself closer (approach) versus pushing it away (avoid). Moreover, the pictures disappeared only upon a full movement in the correct direction, supporting compliance with the instructions. The pictures were presented in a quasi-random order with maximally three consecutive pictures of the same category or format.

Assessment Alcohol-AAT. This version was used during pre- and posttest to assess alcohol-approach tendencies. It consisted of 80 trials. In these, each of the 20 pictures had to be pulled twice and pushed twice, depending on picture orientation. This yielded 20 responses each for the four conditions of pull-alcohol, push-alcohol, pull-non-alcohol, push-non-alcohol. The task started with 13 practice trials showing neutral objects. As in previous studies, an AAT score was computed for each patient from the 80 experimental trials of his or her pretest, after excluding extreme outliers from the reaction times (RTs; the fastest 1% and the slowest 1% of all responses). This AAT ApB score was computed as the difference between the median RTs for alcohol trials (push-alcohol minus pull-alcohol), minus the corresponding difference for non-alcohol trials (push-non-alcohol minus pull-non-alcohol). Positive values of this difference score indicate a relative tendency to approach alcohol pictures. The same score was computed for the RTs of the AAT posttest. The internal consistency of these scores was determined by computing each participant's AAT score for each picture and by computing Cronbach's alpha for these values. The internal consistency of the scores was low but in the upper range of what is usually reported for RT tasks (Cronbach's alpha = .58 for the pretest and .55 for the posttest). The retest reliability (computed for 143 patients in the no-training group only) was nonexistent, however ($r = .01$, $p = .93$). In addition, a change score (posttest minus pretest) was computed from these two scores. Negative values of this AAT change score indicate change in the intended direction, that is, a reduction of the alcohol ApB.

Active AAT training. This modified version of the AAT was administered in each of the training sessions involving active AAT training, using the same pictures as in the assessment version. The training effect was achieved by presenting all alcohol pictures in the to-be-pushed landscape format and all nonalcohol pictures in the to-be-pulled portrait format. Per session, 200 training trials were presented (100× push-alcohol, 100× pull-non-alcohol), with a short break halfway through. The first training session started with 12 practice trials, whereas the other sessions did not contain practice trials.

Sham AAT training. Participants receiving sham AAT training completed this version in each of their AAT training sessions. It was identical to the active AAT training, except that both alcoholic and nonalcoholic beverages were both approached and avoided (for each session: 50× pull-alcohol, 50× push-alcohol, 50× pull-non-alcohol, 50× push-non-alcohol).

General aspects of the Alcohol-DPT. The Alcohol-DPT was designed to measure and/or modify early vigilance for alcohol-related stimuli, using the same pictures and response movements as in the AAT. In the DPT, a series of picture pairs was presented to the patients. Each pair consisted of an alcoholic beverage and a nonalcoholic one, using the same pictures as in the AAT. The two pictures were presented side-by-side, being approximately 12 cm high and 8 cm wide, with approximately 12 cm of space between them. After 500 ms, the pictures disappeared automatically, and one of them was replaced by a small letter (approx. 0.5 cm high). If it was the letter S (as in the German word "Schieben," meaning push), participants had to respond by pushing the joystick away from themselves. If the letter Z was presented instead (as in the German word "Ziehen," meaning pull), they had to pull the joystick closer. Upon a full joystick movement in the correct direction, the letter disappeared and the next trial could be started. We opted for the joystick rather than the usually employed computer keyboard as the response device to ensure comparable response behavior in the AAT and the DPT (cf. Sharbanee, Stritzke, Wiers, & MacLeod, 2013). Importantly, however, no zoom function was used in this task, and the response direction was unrelated to picture contents: Half of the alcohol pictures were replaced by S letters and half by Z letters, and the same was true for the nonalcohol pictures. Moreover, the joystick movement made the small letter disappear, not the pictures. Thus, there was no association between picture contents and approach-avoidance responses. Instead, the association between picture contents and letter *location* was manipulated: The letters always replaced the nonalcohol pictures (in the active DPT training) or both picture types equally often (in the assessment DPT and the sham DPT training).

Assessment Alcohol-DPT. This version was used during the pretest and the posttest to measure early vigilance for alcohol pictures before versus after training. It consisted of a total of 80 trials. Each trial consisted of an alcohol-nonalcohol picture pair followed by a letter, and each combination of probed picture (alcohol or nonalcohol) and letter (S or Z) occurred 20 times. The position of the pictures (alcohol left or right) and the letters (left or right) were fully counterbalanced. This yielded 40 trials in which the letter replaced the alcohol picture and 40 trials in which it replaced the nonalcohol picture. As for the AAT, we first excluded extreme outliers from the RTs (the fastest 1% and the slowest 1% of all responses). For the DPT pretest, a DPT score was then computed for each patient as the median RT of responses to the 40 letters that replaced the nonalcohol picture minus the median RT of responses to the 40 letters that replaced the alcohol picture. Positive values of this difference score indicate an alcohol AtB. The same score was computed for the RTs of the DPT posttest. The retest reliability of the scores (computed for 136 patients in the no-training group only) was low, as it usually is for RT tasks ($r = .31$, $p < .001$). The internal consistency of the DPT scores was determined by computing each participant's DPT score for each of the 10 picture pairs and by computing Cronbach's alpha for these

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values. Unfortunately, the internal consistency of the scores was extremely low (Cronbach's alpha = .02 for the pretest and −.02 for the posttest). Finally, a change score (posttest score minus pretest score) was computed. Negative values of this DPT change score indicate change in the intended direction, that is, a reduction of the alcohol AtB.

Active DPT training. This version was administered in each of the training sessions involving active DPT training. In each training trial of this version, the letter S or Z occurred in the location of the previously presented picture of a nonalcoholic drink, never in the location of the alcoholic drink. Per session, 200 training trials were presented (50× S left, 50× S right, 50× Z left, 50× Z right), with a short break halfway through. The first training session started with 24 practice trials, whereas the other sessions did not contain practice trials.

Sham DPT training. Participants receiving sham DPT training completed this version in each of their DPT training sessions. It was identical to the active DPT training, except that the letters replaced the alcoholic and the nonalcoholic picture equally often. This also yielded 200 trials (50× S left, 50× S right, 50× Z left, 50× Z right) with a short break halfway through, but without any contingency of picture contents and probed location.

Experimental Training Groups

The study was designed as an RCT, and a total of 1,405 patients were randomly assigned to one of five experimental groups using unequal randomization: The (1) "active AAT group" received six sessions of active AAT training (n = 238), whereas the (2) "active DPT group" received six sessions of active DPT training (n = 230). The (3) "active 3 + 3 group" also received a total of six sessions, namely, three sessions of each active training variety (n = 255). For additional counterbalancing, approximately half of the patients in this group (again randomly assigned) started with three sessions of AAT training followed by three sessions of DPT training, whereas the others performed the opposite order. The oversampled (4) "sham training group" received only the corresponding sham versions of the training methods, that is, six sessions of sham AAT training (n = 109), six sessions of sham DPT training (n = 110), or 3 + 3 sessions of each sham training (n = 97). Again, patients were randomly assigned to one of these subgroups. Finally, the similarly sized (5) "no-training group" did not receive any training between pretest and posttest (n = 366). Importantly, active training methods and sham training methods were never mixed: Each patient received either only active training methods, only sham training methods, or no training at all. Patients were blinded to the difference between active versus sham training by receiving plausible training rationales for both versions and by being led to believe that they received a training tailored to their individual needs.

Research Questions and Hypotheses

All analyses used two-sided tests with p = .05. The primary outcome variable, "status at 1-year follow-up," was analyzed following a hypothesis-driven approach, testing five distinct hypotheses: First, we hypothesized that (1) sham training would not reduce relapse rates compared to no training, justifying a combined control group. Second, we hypothesized that (2) active AAT training, (3) active DPT training, and (4) active AAT-DPT training would all yield lower relapse rates than the combined control group. Given that approach-bias modification and attention-bias modification may tap into separate processes (Sharbanee et al., 2013), we also hypothesized that (5) the combined AAT-DPT training would yield lower relapse rates than AAT training and DPT training. A similar hypothesis-driven approach was used for the manipulation checks reported below, which addressed how AAT training, DPT training, and AAT-DPT training affected the AAT scores and DPT scores measured during pretest and posttest. Finally, we aimed to replicate the moderation and mediation effects reported by Eberl et al. (2013). First, we expected mediation: A larger training-induced decrease of the targeted bias would predict a reduced relapse probability. Second, we expected moderated mediation: a stronger change in cognitive bias for those with a stronger bias at pretest. Third, we expected moderation regarding the clinical outcome, such that older patients would profit more from AAT training and DPT training.

Results

Treatment Outcome: Effects of Training Methods on 1-Year Follow-Up Outcome

Overall, 80.8% of the patients in the three active training groups finished the prescribed six sessions of training. Clinical outcomes at follow-up were obtained from 78.9% (1,108 of 1,405) of the patients, and the overall success rate was 48.8%. Success rates per group are shown in Table 1; these are based on the ITT analysis involving all 1,405 patients. Confirming our first hypothesis, the sham training control group did not show a higher success rate than the no-training control group, $\chi^2(1) = .28$, $p = .60$, $\phi = .02$ (see Table 1), justifying the use of a combined control group. Moreover, the success rates of the three sham training subgroups did not differ from each other either, $\chi^2(2) = 3.94$, $p = .13$, $\phi = .11$. As predicted, the AAT training yielded a higher success rate than the control conditions, $\chi^2(1) = 4.18$, $p = .041$, $\phi = .07$, and so did the DPT training, $\chi^2(1) = 8.04$, $p = .005$, $\phi = .09$. The combined AAT-DPT training, however, yielded only a marginally higher success rate than the control conditions, $\chi^2(1) = 3.6$, $p = .058$, $\phi = .06$. In contrast to our last hypothesis, the success rates of the three active training groups did not differ significantly from each other, $\chi^2(2) = .79$, $p = .67$, $\phi = .03$ (see Table 1). These results indicate that all active training methods had a small but robust long-term effect, without revealing a specific advantage of AAT training, DPT training, or their combination. We also computed analyses according to DGSS-1 criteria (including only the 1,108 patients reached at follow-up) and per-protocol analyses including only the 956 patients who both completed the training and were reached at follow-up. These analyses showed that relapse rates were significantly lower in all three active training groups than in the combined control group. These analyses, as well analyses including only those 750 patients for whom pretest data and posttest data were available, are included in the online supplemental materials.

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Manipulation Checks: Effects of AAT Training and DPT Training on ApB and AtB for Alcohol

To test whether active training affected patients' alcohol-related biases, their pretest scores were compared to their posttest scores (see Table 2). Unfortunately, for several reasons, AAT pretest data were available from only 1,063 patients, posttest data from only 926 patients, and complete AAT data sets from only 774 of the 1,405 patients. Similarly, DPT pretest data were available from only 1,075 patients, posttest data from only 936 patients, and complete DPT data sets from only 773 of the 1,405 patients. Moreover, only 705 patients had both complete AAT data sets and complete DPT data sets and could be entered into the analyses reported below. This group of 705 patients contained significantly more females and was significantly older than the group of patients with incomplete data, but the two groups did not differ on any of the alcohol-related variables shown in Table 1. The main reason for data loss was experimenter error in dealing with the clinic's policy regarding privacy and data security. The policy requires the nightly deletion of all data saved on the computers of the clinic, including the ones used for this study. Unfortunately, relatively often the pretest and posttest data were not saved onto other media before they were erased. In addition, computer problems sometimes prevented correct execution of the AAT or correct storage of the data, or patients sometimes did not show up for pretest or posttest. Moreover, several patients were dismissed from the clinic before they could complete the posttest (usually because they relapsed during treatment). This limitation should be kept in mind when interpreting the results reported below, which are based on half of the sample only.

First, we found that before training, the group of 705 patients showed neither an ApB nor an AtB for alcohol. In fact, there was a nonsignificant avoidance tendency (−7 ms, $SD = 106$ ms, $t(704) = 1.77$, $p = .08$) at pretest and a significant AtB away from alcohol (−6 ms, $SD = 68$ ms, $t(704) = 2.34$, $p = .02$). These two biases were uncorrelated, $r = .03$, $p = .49$.

Following the hypothesis-driven analysis approach described above, we first compared the change scores of the two control groups to each other. As predicted, they did not differ from each other, neither for the AAT change scores, $t(322.4) = 1.01$, $p = .32$, nor for the DPT change scores, $t(324) = .05$, $p = .96$; therefore, they were merged into a single control group (see Table 2). Second, the AAT training group was compared to the combined control group: After six sessions of AAT training, the change in AAT scores of −24 ms was marginally larger than the control group's change of 1 ms, $t(339.3) = 1.91$, $p = .057$. The two groups' changes in DPT scores did not differ from each other, $t(233.2) = .56$, $p = .58$. These results suggest that AAT training had a marginal effect on AAT scores at best and no effect on DPT scores. Third, the DPT training group was compared to the combined control group: Their reduction in AAT scores of −31 ms was significantly larger than the control group's change of 1 ms, $t(468) = 2.23$, $p = .03$. Moreover, the DPT groups' DPT scores increased by 8 ms, compared to an increase of 23 ms in the control group, $t(468) = 1.66$, $p = .097$. Thus, DPT training had an effect on both AAT scores and DPT scores. Regarding the latter, however, DPT training did not decrease the attention bias as intended; it only reduced the undesired increase of the bias that occurred in the control group. Fourth, the combined AAT-DPT training was compared to the combined control group: AAT-DPT training reduced the AAT scores by −32 ms, which differed significantly from the control group's value of 1 ms, $t(482) = 2.34$, $p = .02$. Moreover, the training yielded an increase of 4 ms in the DPT scores, which was significantly smaller than the control group's increase of 23 ms, $t(350.4) = 2.52$, $p = .012$, mirroring the effects of the DPT training.

Amount of Bias Change as Mediator of Treatment Success

The results reported so far suggest that the three active training methods tended to cause a larger reduction of the alcohol-related cognitive biases than observed in the control group and that they caused a significantly higher success rate at 1-year FU. Therefore, we aimed to test whether the size of the bias change mediated the effect of training on clinical outcome, such that a larger training-induced reduction of the bias (e.g., from alcohol-approach to alcohol-avoidance) would predict a higher chance of treatment success. These analyses must be considered exploratory, given the limited number of participants for whom complete pretest and posttest data were available and given the low reliability of the scores. It turned out that the preconditions for the mediation analysis were not met because the potential mediators did not predict treatment outcome (MacKinnon, 2008). In an analysis of the complete sample, this was true for both the AAT change scores ($r = .02$, $p = .58$, $n = 774$) and the DPT change scores ($r = -.02$, $p = .63$, $n = 773$). The same was found for the AAT change scores when patients receiving active DPT training were excluded

Table 2
Mean AAT Scores (With SDs) and Mean DPT Scores (With SDs) in Pretest and Posttest

Variable	6× AAT training	6× DPT training	3 + 3 training	Sham training	No training	Combined control
AAT scores	*n* = 145	*n* = 145	*n* = 159	*n* = 185	*n* = 140	*n* = 325
Pretest	−13 (100)	8 (111)	−3 (103)	−7 (101)	−19 (125)	−10 (112)
Posttest	−37 (84)	−23 (103)	−35 (84)	−14 (82)	−4 (108)	−9 (94)
Pre–post change	−24 (120)	−31 (132)	−32 (133)	−7 (129)	10 (172)	1 (145)
DPT scores	*n* = 146	*n* = 144	*n* = 157	*n* = 190	*n* = 136	*n* = 326
Pretest	−8 (71)	1 (72)	−1 (67)	−8 (66)	−12 (70)	−10 (68)
Posttest	9 (82)	9 (65)	3 (58)	15 (63)	11 (80)	13 (70)
Pre–post change	17 (108)	8 (92)	4 (75)	23 (86)	23 (88)	23 (87)

Note. Positive AAT scores indicate an alcohol-approach tendency, positive DPT scores indicate an attention bias for alcohol, and negative change scores (posttest minus pretest) indicate change in the intended direction. AAT = approach-avoidance task; DPT = dot-probe task.

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($r = -.03$, $p = .53$, $n = 470$) and for the DPT change scores when patients receiving active AAT training were excluded ($r = -.01$, $p = .77$, $n = 470$). Thus, mediation of the effect of training methods on treatment outcome by changes in the targeted cognitive processes was not confirmed.

Pretest Bias as a Moderator of Mediation

To assess whether the amount of bias change was moderated by the level of pretest bias (e.g., such that the active trainings caused a larger decrease in bias for patients who started out with a larger bias before training), we computed Oldham's correlation (see Equation 3 in Tu & Gilthorpe, 2007) separately for the AAT scores and the DPT scores. The main advantage of Oldham's correlation is that it corrects for two mathematical biases, namely, mathematical coupling and regression to the mean, thereby yielding a less biased estimate of the correlation underlying a moderation effect (see Snider, Quisenberry, & Bickel, 2016). According to Snider et al. (2016), values of Oldham's correlation above the conventional medium effect size of $r = .30$ should be considered evidence for the presence of moderation. For the AAT scores, Oldham's correlation was $r = .146$ ($p < .001$), and for the DPT scores, it was $r = -.012$ ($p = .758$). Although the correlation was significant for the AAT scores, both values fell below the conventional level of $r = .30$ and therefore provide no evidence for the hypothesized moderated mediation. This is in contrast to the results reported by Eberl et al. (2013). We computed Oldham's correlation for the pre–post data reported by Eberl and colleagues, which yielded an Oldham's correlation of $r = -.427$. Thus, the results reported by Eberl et al. (2013) hold, even after correcting for the mathematical biases, while the current results do not replicate them.

Age as Moderator of Training Effects on Clinical Success

To test for moderation of the effect of AAT training on clinical success, we divided the patients into three similarly sized groups according to their age. We then used logistic regression to estimate the effects of training group (AAT training vs. combined control) and age group as well as their interaction on status at 1-year FU. While both training group and age group were significant predictors of clinical success (with higher success rates for older patients and patients receiving AAT training), their interaction was not a significant predictor, $\beta = .03$, $p = .61$. Thus, the AAT training reduced relapse rates independently of the patients' age. Comparable results were observed in a second logistic regression that estimated the effects of DPT training (DPT training vs. combined control) and age group as well as their interaction on status at 1-year FU. As before, the interaction of training group and age group was not a significant predictor, $\beta = -.09$, $p = .34$. Thus, both AAT training and DPT training reduced relapse rates independently of the patients' age, and the moderation reported by Eberl et al. (2013) was not replicated.

Discussion

The main goal of the present large-scale RCT was to assess the clinical effects of two varieties of CBM, retraining of AtB, ApB, or both. A previously successful alcohol-related ApB modification (AAT training; Eberl et al., 2013; Manning et al., 2016; R. W. Wiers et al., 2011), a new version of AtB modification (DPT training; Schoenmakers et al., 2010), and a combination of both were employed to reduce relapse rates at 1-year FU in abstinent, alcohol-dependent inpatients. The 1-year success rates of these three active training methods were compared to each other and to those of two control groups receiving either sham trainings or no training at all. We found that success rates of the groups who had received an active training method were significantly higher than success rates of the control groups. Moreover, the low success rates of the two control groups did not differ from each other; neither did the higher success rates of the three active training groups. Thus, DPT training was as effective as AAT training, and the combination of both training methods did not increase success rates further.

Regarding our secondary process-related results, the effect of AAT training on the alcohol ApB was small in size and only marginally significant, and the same was true for the effect of DPT training on the alcohol AtB. Only the combined AAT-DPT training had a significant effect on both the AtB and ApB. In addition, we did not find a significant mediation of the clinical effect by the change in trained bias, nor did we find moderation of the mediation by the amount of pretest bias. Finally, we did not replicate moderation of the clinical outcome by age (Eberl et al., 2013).

Our primary result, the clinical effect observed for the AAT training, replicates earlier findings (Eberl et al., 2013; Manning et al., 2016; R. W. Wiers et al., 2011) and adds to the growing body of evidence for the usefulness of this type of CBM in clinical samples in addiction (see Kakoschke et al., 2017; R. W. Wiers et al., in press). When combined with standard treatment, active CBM reduced relapse 1 year later with 8.4% (number needed to treat = 12; comparable to the most effective of current medications used for alcohol use disorder, acamprosate; Jonas et al., 2014), which is almost identical to the 8.5% reported by Eberl et al. (2013). However, this number is considerably lower than the 13% reported by R. W. Wiers et al. (2011) and the 22% reported by Manning et al. (2016). The most likely interpretation is that the 8.5% is the most realistic estimate of the effect, as this was found in the two larger studies. However, an alternative interpretation is that CBM may be more effective when provided during detoxification (Manning et al., 2016) or closely after detoxification (R. W. Wiers et al., 2011). This suggestion could be investigated systematically in future research.

The clinical effect observed for the DPT training is more novel and extends earlier results in a patient sample reported by Schoenmakers et al. (2010). However, it contrasts with more negative findings reported by Clerkin and colleagues (2016), who tested a double DPT training in socially anxious alcohol-dependent individuals recruited from the community: participants received both alcohol DPT training (real/sham) and social anxiety DPT training (real/sham). Some effects were found on the AtB but no differential effects on clinical alcohol-related outcomes. Lack of statistical power is a likely explanation (86 participants in four groups). Two other RCTs tested the effects of a different form of AtB modification, a pictorial Stroop-based attentional control training with increasing levels of difficulty (Fadardi & Cox, 2009). While the original paper used a baseline-control method (no control group), in a later study, Cox and colleagues (2015) tested the effects of this AtB modification program in harmful drinkers, combined with

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motivational counseling (both interventions, compared to no intervention in a 2 × 2 between-subjects design). Results showed a short-lived marginally significant effect on reduced drinking of the AtB modification and a more long-lived effect of the motivational intervention. Finally, an Internet-based RCT compared this version of AtB modification to different varieties of ApB modification in self-identified problem drinkers (R. W. Wiers et al., 2015) and found reduced drinking in all groups, including the sham training group. This nonspecific effect is often found in Internet trials, as well as in other domains (see Price et al., 2016; R. W. Wiers et al., in press).

The current study is one of the first to combine two different CBM approaches in a patient sample, targeting two different cognitive biases: AtB and ApB. We expected this combination to be most effective in terms of relapse prevention because it targets two relevant processes that are relatively independent (Sharbanee et al., 2013), therefore leaving room for additive effects. However, it should be noted that other studies did find correlations between alcohol AtB and ApB, after drinking alcohol in heavy drinkers (Schoenmakers, Wiers, & Field, 2008) and in alcohol-dependent patients (C. E. Wiers et al., 2017), indicating that the processes may be correlated under certain conditions. The combined AAT-DPT training reduced relapse rates as much as the single-training varieties did but not more strongly. An explanation could be the limited number of three training sessions of each training type involved. Keeping the overall number of training sessions constant across groups was necessary to avoid a confound of training type and overall training dose in the current study. However, this might have reduced the number of sessions per training too much for some participants, particularly for those who did not complete all six sessions, given that analyses of learning curves in AAT training indicated six sessions as a median optimal number (with much variance, Eberl et al., 2014). Therefore, future studies could also test effects of a 6 + 6 combined training group. Related to this, future studies could systematically explore dose-response relations of training and adapt the training dose to individual needs. However, although theoretically an important way forward, we do note that the poor reliability of the current assessment instruments may make this difficult.

Our secondary results relate to the biases observed before and after training. With regard to the manipulation checks, our results revealed only hardly any evidence for effects of the AAT training or the DPT training on the targeted biases. Unfortunately, the data set for these analyses was much smaller than the data set for the clinical effects, related to the practicalities of the clinical setting of the research (see limitations below). Compared to the control groups, the AAT training reduced the patients' alcohol-approach bias (with a small effect size), in line with earlier results (R. W. Wiers et al., 2011). The effect of the DPT training was different: It did not reduce the preexisting AtB for alcohol, but it tended to prevent the increase in bias that occurred in the control groups. An increase in AtB during treatment has been reported before (Schoenmakers et al., 2010) and may reflect a slow incubation of returning desire for alcohol. Note that an AtB can occur for appetitive and feared stimuli (Field et al., 2016); it would therefore be interesting to assess the affective evaluation of these stimuli (in an implicit and explicit way) as a moderator of this effect.

Our secondary analyses of potential transfer effects revealed an effect of the DPT training on ApB but no effect of the AAT training on AtB. This latter null result may be explained by the poor internal consistency of the AtB scores. It is similar to what Field et al. (2007) and Sharbanee et al. (2013) reported for alcohol training, as well as Elfeddali, de Vries, Bolman, Pronk, and Wiers (2016) for CBM in smoking, suggesting bias-specific training effects. However, this similarity may be limited to addictions, given that Becker et al. (2016) found transfer effects of a general positivity-approach training to attention bias. In general, the question of how the modification of one bias affects other biases, including biases in attention, action-tendencies, interpretation, and memory, deserves more research but is currently hindered by the lack of reliable outcome measures. This issue is also theoretically interesting: To what extent is there a common neurocognitive mechanism involved in overcoming motivationally biased response tendencies (cf. C. E. Wiers & Wiers, 2017)?

Regarding factors that moderate the effects of CBM on clinical outcomes, there are also important open questions: For the AAT training, we could not replicate earlier findings (Eberl et al., 2013) suggesting that the AAT training reduced relapse rates most for older patients. Moreover, the effect of the DPT training was independent of age as well. However, this observed lack of moderation may be due to unreliable pretest measures, and it should be investigated further. In general, the most important challenge for research into CBM's mechanisms is to develop more reliable indices of the biases, using more reliable tasks as an outcome measure (e.g., the more reliable Implicit Association Task; R. W. Wiers et al., 2011), other algorithms for the DPT (e.g., Zvielli, Bernstein, & Koster, 2015; but see Kruijt, Field, & Fox, 2016), or other indices like eye movements (Field, Munafò, & Franken, 2009) or functional MRI (C. E. Wiers et al., 2015).

Finally, our secondary analyses did not confirm the hypothesis that the effect of CBM on the clinical outcome would be mediated by the size of the bias change or that this mediation would be moderated by the size of the preexisting bias. Thus, we cannot conclude that a larger training-induced reduction of the bias (i.e., from alcohol-approach to alcohol-avoidance, or from early vigilance for alcohol to early vigilance for nonalcohol) would generally predict a higher chance of treatment success or that this would be true particularly for patients with a larger pretraining bias. These null findings are similar to what R. W. Wiers et al. (2011) reported but unlike the results found by Gladwin et al. (2015) and Eberl et al. (2013). Most likely, our null findings also are due to the low reliability of the pretest and posttest measures of ApB and AtB, as the positive findings were observed with a more reliable measure (Approach-Avoid Implicit Association Test).

As every study, this one also has a number of limitations worth noting. Many of them relate to the fact that the study was conducted as an RCT in the context of a large clinic. First, it is quite unfortunate that complete pre- and posttest data were available for less than 50% of the participants. This seriously limited both the validity and statistical power of our analyses of training effects and of the mediation analyses. The effect of this problem was further amplified by the low reliability of the AAT and DPT measures. Regarding the latter, it may have been unfortunate to use the joystick for responding, rather than the keyboard that is usually employed. As intended, using the joystick for both trainings reduced technical problems and increased the comparability of the AAT training and the DPT training. The DPT assessment used here lacked internal consistency, but that has also been observed with the more standard keyboard versions (Ataya et al., 2012), and the version used here did have a significant test–retest reliability. Future studies should probably better use other indices of alcohol AtB, such as eye movements (Field et al., 2009). Moreover, as mentioned above, our choice to keep the total number of training sessions constant for all active training groups may have underestimated the additive effects achieved by a combination of AAT training and DPT training. Therefore, future studies could also include a combined training group that receives six sessions of each training. Finally, it should be noted that the positive results observed here are limited to a very specific situation, namely, CBM as an add-on treatment for abstinent adult alcohol-dependent patients, intended to prevent relapse. As promising as the current results are, they do not imply similar effects in other situations, for instance, when it comes to reducing alcohol consumption in college students unmotivated to change their drinking (Lindgren et al., 2015; see also Wiers et al., in press). Finally, a more fine-grained measure of alcohol use after treatment discharge could be interesting, but in the present clinical context, we could only obtain the standardly used 1-year follow-up outcomes. A more fine-grained measure could also be used to test to what extent CBM may help to achieve reduced drinking as a potential outcome instead of abstinence (Hasin et al., 2017).

Despite these limitations, when compared to many other CBM studies, the current study has a number of important strengths. It was designed as a large-scale RCT, involving three active training groups and both a sham training control group and a no-training control group. This was only possible because of the large sample available at the clinical research site, the salus clinic Lindow. Unfortunately, large clinical samples are rare in CBM research, which usually prevents the detection and replication of small effects like the one observed here and in previous studies (Rinck, 2017). Moreover, the high FU return rates achieved by the clinic allowed for a more powerful test of the clinical effect. Because of these advantages, the current study could show that both AAT training and DPT training reduced relapse rates in abstinent alcoholics, with a small but significant effect. For AAT training, this replicates earlier positive results in large samples. Future research will have to show whether the positive results observed for DPT training can also be replicated before it may become a standard add-on to treatment. For both types of CBM, it should also be explored what their exact working mechanisms are, how their effects can be increased further, and how they can be generalized to other situations in the treatment of addictions.

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