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Automatic Approach Behaviors in Alcohol Dependence: Does a Cognitive Bias Modification Training Affect Pavlovian-to-Instrumental Transfer Effects?

Ke Chen[a] Maria Garbusow[a] Miriam Sebold[a, b] Hilmar G. Zech[c]
Ulrich Zimmermann[d, e] Andreas Heinz[a]

[a]Department of Psychiatry and Psychotherapy, Charité Campus Mitte, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [b]Department for Social and Preventive Medicine, University of Potsdam, Potsdam, Germany; [c]Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany; [d]University Hospital, Technische Universität Dresden, Dresden, Germany; [e]Department of Addiction Medicine and Psychotherapy, kbo-Isar-Amper-Klinikum, Munich, Germany

Keywords
Pavlovian-to-instrumental transfer · Alcohol approach bias · Cognitive bias modification · Alcohol dependence · Relapse

Abstract
Introduction: Positively conditioned Pavlovian cues tend to promote approach and negative cues promote withdrawal in a Pavlovian-to-instrumental transfer (PIT) paradigm, and the strength of this PIT effect was associated with the subsequent relapse risk in alcohol-dependent (AD) patients. When investigating the effect of alcohol-related background cues, instrumental approach behavior was inhibited in subsequent abstainers but not relapsers. An automatic approach bias towards alcohol can be modified using a cognitive bias modification (CBM) intervention, which has previously been shown to reduce the relapse risk in AD patients. Here we examined the effects of such CBM training on PIT effects and explored its effect on the relapse risk in detoxified AD patients. ***Methods:*** $N = 81$ recently detoxified AD patients performed non-drug-related and drug-related PIT tasks before and after CBM versus placebo training. In addition, an alcohol approach/avoidance task (aAAT) was performed before and after the training to assess the alcohol approach bias. Patients were followed up for 6 months. ***Results:*** A stronger alcohol approach bias as well as a stronger non-drug-related PIT effect predicted relapse status in AD patients. No significant difference regarding relapse status or the number of heavy drinking days was found when comparing the CBM training group versus the placebo group. Moreover, there was no significant modulation effect of CBM training on any PIT effect or the aAAT. ***Conclusion:*** A higher alcohol approach bias in the aAAT and a stronger non-drug-related PIT effect both predicted relapse in AD patients, while treatment outcome was not associated with the drug-related PIT effect. Unlike expected, CBM training did not significantly interact with the non-drug-related or the drug-related PIT effects or the alcohol approach bias.

Introduction

Pavlovian cues can affect independently acquired instrumental behavior, a phenomenon which is termed Pavlovian-to-instrumental transfer (PIT) effect. This transfer, which has been observed across animals and hu-

Karger@karger.com
www.karger.com/nps

Correspondence to:
Ke Chen, ke.chen@charite.de

mans [1–3], varies according to the Pavlovian background cues, because positively conditioned Pavlovian cues can promote approach behavior and reduce withdrawal, while negatively conditioned cues tend to promote withdrawal and reduce approach [4]. In a general PIT paradigm, Pavlovian cues associated with reward are presented while an individual performs instrumental behavior to obtain a different reward; presentation of such background cues that have previously been paired with a reward increases the instrumental approach behavior to the different reward [5]. In a specific PIT paradigm, it is assessed whether Pavlovian background cues that have been associated with a specific reward promote instrumental behavior that aims at obtaining this specific reward [3, 6]. Rodent studies have indicated that drug exposure can induce general alterations in reward learning processes, with findings that ethanol-related cues promoted general PIT in ethanol-treated rats [5] and enhanced non-drug-related PIT effects were observed in cocaine-treated rats [7] and mice under chronic alcohol exposure [8]. Recent studies that aimed to translate these findings to humans showed that a PIT effect using Pavlovian conditioned stimuli that were previously associated with monetary reward is increased in alcohol-dependent (AD) patients compared to healthy controls [9, 10]. Regarding treatment outcome, both the strength of the behavioral non-drug-related PIT effect and PIT-related functional activation in the left nucleus accumbens were increased in prospectively relapsing versus abstaining patients [9, 11]. Moreover, high-risk social drinkers were shown to exhibit enhanced PIT effects compared to low-risk social drinkers [12, 13]. Using a different paradigm with alcohol-associated cues, multivoxel pattern analysis revealed that the neural drug-related PIT activation pattern could predict future relapse among detoxified AD patients with 71.2% accuracy [14]. Specifically, using background alcohol versus water cues in this PIT paradigm inhibited instrumental approach among AD patients who subsequently abstained but not among future relapsers [15]. These findings indicate that proneness to relapse may be associated with the extent to which Pavlovian cues interact with instrumental inhibition. An imbalance between automatic go processes and controlled no-go processes could also lead to approach biases to alcohol in AD patients and heavy drinkers, which can be reflected in longer response latency to avoid versus approach alcohol stimuli [16–18].

In recent decades, a growing number of studies have tried to modulate approach bias among persons with alcohol dependence by means of cognitive bias modification (CBM) trainings (hereafter, we used the term CBM training to refer exclusively to alcohol approach bias retraining). In its most common form, this CBM intervention adapts the alcohol approach-avoidance task (aAAT) [e.g., [19–24]], which is usually used to test an automatic approach bias to alcohol-related stimuli. Wiers et al. conducted the first randomized placebo-controlled clinical study using a CBM intervention targeted at the alcohol approach bias [19]. In that study, AD patients who received CBM training learned to increase avoidance behavior to alcohol stimuli. After training, the approach bias was reversed and patients tended to now show an alcohol avoidance bias. Moreover, patients receiving the training displayed better treatment outcomes 1 year later [19]. In line with this finding, several other studies also observed promising CBM effects on decreasing the automatic alcohol approach bias and improving treatment outcomes (e.g., lower relapse rate, longer abstinent time) [20, 23–28], or reducing alcohol consumption [29]. On the neural level, CBM training reduced the activation related to the alcohol approach bias in the medial prefrontal cortex [30]. However, a recent systematic review revealed that significant training effects may be limited to persons with more severe forms of alcohol dependence [31].

To date, the underlying mechanisms of CBM interventions are still insufficiently understood. Previous research found that CBM training alters implicit alcohol approach associations as measured by an implicit association task (IAT) [19, 32]. Moreover, CBM training reduced neural cue reactivity in the bilateral amygdala and behavioral arousal ratings of alcohol-related stimuli in AD patients [21]. These findings indicate that the approach tendency to alcohol cues targeted in CBM training may impact other alcohol cue-related effects e.g., in PIT with drug-related stimuli. A dual-process model suggests that CBM training targets an automatic approach bias, which manifests when appetitive stimuli activate an automatic and rather "impulsive" system, which cannot be overridden by low cognitive control [33]. The strength of the non-drug PIT effect in AD patients was also associated with impulsivity measured with a delay discounting task [10], and impairments in inhibiting automatic approach biases to appetitive Pavlovian stimuli in this task predicted a poor prospective treatment outcome [34, 35]. The alcohol approach bias and the non-drug PIT effects may thus reflect potentially related aspects of impulsivity. In accordance with these considerations, we observed a significant correlation between the alcohol approach bias and the non-drug PIT effect [36].

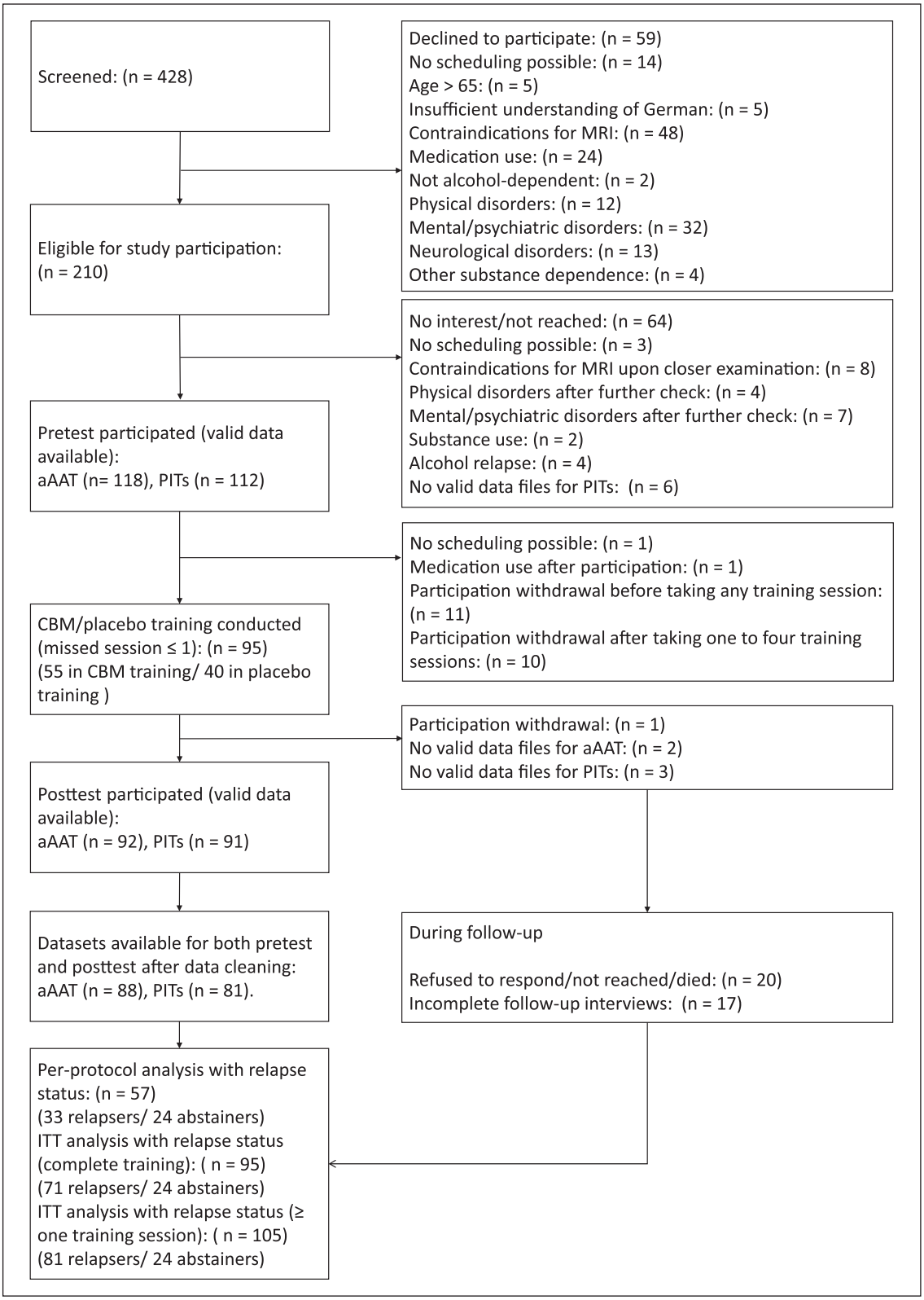

Fig. 1. The flow chart of sample sizes and reasons for exclusion at different study stages. aAAT, alcohol approach/avoidance task; CBM, cognitive bias modification; ITT, intention-to-treat; MRI, magnetic resonance imaging; PIT, Pavlovian-to-instrumental transfer.

We therefore investigated whether CBM training affects general approach tendencies as associated with the non-drug PIT effect as well as alcohol cue-related PIT effect. We also assessed whether we can replicate a significant effect of CBM training on the alcohol approach bias in AD patients. We furthermore explored effects on the prospective risk of relapse among AD patients in the CBM training group versus the placebo group. An aAAT paradigm adapted from Wiers et al. [19] was applied to measure the alcohol approach bias, and we used both the non-drug-related PIT task described by Garbusow et al. [9] and the drug-related PIT task described by Schad et al. [15]. The CBM training was adapted from the aAAT to implicitly train patients to avoid alcohol stimuli and approach soft drink stimuli. We used an irrelevant – feature CBM program (i.e., participants respond to the unrelated feature of the stimuli (in our study, the tilt of the stimuli) rather than to stimulus contents), in order to make it comparable to most studies that applied alcohol approach retraining and found significant training effects (e.g., [20, 24, 25, 32]).

In the CBM training condition, all alcohol cues were to be rejected, while in the placebo training condition, alcohol cues were equally often to be rejected and to be approached. The aAAT and PIT tasks were conducted before and after the training procedure. Patients were followed up for 6 months after study participation. We hypothesized that after training, patients in the CBM training group would show (1) a decreased alcohol approach bias, (2) a decreased non-drug relate-PIT effect, and (3) increased inhibition of instrumental approach elicited by alcohol-related background cues in drug-related PIT, while no changes would occur in the placebo group. Furthermore, we explored whether CBM training will decrease the relapse risk or the number of heavy drinking days in AD patients.

Materials and Methods

Participants

The study was carried out from April 2015 to August 2018 for the primary outcome data collection, and follow-ups were conducted until February 2019. $N = 210$ patients were included after screening, in which $n = 95$ AD patients who completed the training (93 patients finished all six training sessions, and 2 patients missed one training session) were included in the per-protocol analysis. Six CBM training sessions have been shown to provide optimal effects [25]. Ten patients who did not complete the training but participated in at least one training session were included in an additional intention-to-treat (ITT) analysis [37]. The sample size and reasons for exclusion at each study stage are shown in Figure 1. Of the 95 patients included in the per-protocol analysis, $n = 55$ were assigned to the CBM training group and $n = 40$ patients to the placebo training group. This study focused on whether there is a CBM training effect on PIT task performance. Given that there are no previous studies examining CBM effects on PIT, we assume a similar effect size for this purpose as reported for CBM effects on the alcohol approach bias itself, when assuming that alcohol approach bias is mediated by Pavlovian effects on instrumental approach behavior. Previous studies showed a moderate effect size ($\eta^2 = 0.05–0.06$) [19, 20, 38]. To observe a small to moderate effect size ($\eta^2 = 0.05$) with a power of 80%, a minimum of $n = 40$ subjects in total are needed. The sample size of our study ($n = 81$ for PIT analysis) was accordingly powered for the aim of detecting a CBM effect on behavioral PIT.

The data were collected as part of a bicentric study conducted in Berlin and Dresden, Germany (Learning and Alcohol Dependence, LeAD study, https://ssl.psych.tu-dresden.de/lead/; clinical trial number: NCT02615977). Participants received a monetary compensation of 10 EUR per hour for participation and the wins from the PIT tasks and unrelated decision-making tasks.

AD patients were recruited during detoxification. Patients fulfilled a diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), which was assessed by the computerized Munich Composite International Diagnostic Interview (M-CIDI) [39, 40]. All patients were between 18 and 65 years old, and had sufficient understanding of German language. Patients had abstained from alcohol after detoxification for a median of 21 days at the time of study participation, and had low severity of withdrawal symptoms for three consecutive days measured by the Clinical Institute Withdrawal Assessment for Alcohol revised version (CIWA-Ar score <4) [41]. Other substance dependence except for alcohol and nicotine would lead to exclusion. Current alcohol consumption or substance use revealed by breath and urine testing would also lead to exclusion. Patients had no neurological disorders or major psychiatric disorders according to M-CIDI. Patients did not take any medication or drug known to interact with the central nervous system within four half-lives post last intake, including the detoxification treatment before study participation. In addition, contraindications to MRI also led to exclusion as fMRI tasks are part of the large study. Sample characteristics of participants in the two training groups are listed in Table 1.

Procedure

The CBM or the placebo training was scheduled every other day (with 3 days intermission over the weekend), so that the whole training procedure could be completed within 2 weeks. Some participants (24%) required rescheduling because of personal reasons, e.g., due to intervening somatic complications. In the end, participants finished the CBM or the placebo training within a mean of 12.6 days (SD = 6.1 days; range = 6–43 days). Both the aAAT and the two PIT tasks were conducted before and after the CBM procedure. Follow-up interviews were conducted every 4 weeks by telephone or in person in a 6-month period (telephone interviews at week 6, 10, 18, 22 after the first training session, and in-person interviews at week 14 and 26) to retrospectively assess alcohol consumption in patients using the timeline follow-back [46]. The timeline of the study procedure is shown in Figure 2. The sample characteristic comparisons between participants who completed training sessions within 2 weeks and who took longer than 2 weeks,

Table 1. Sample characteristics of AD patients in two training groups

	CBM training group	Placebo training group	*p* values
Gender	female: 11; male: 44	female: 6; male: 34	0.53[a]
	Mean (SD)	Mean (SD)	
Age	48.02 (9.89)	46.50 (10.02)	0.49[b]
Education, years	15.04 (3.29)	15.25 (4.01)	0.75[b]
Smokers, *n* (%)	65	78	0.18[a]
Alcohol dependence severity (ADS score)	17.00 (8.43)	18.30 (7.82)	0.34[b]
Abstinence before study, days	24.19 (14.13)	22.43 (13.62)	0.53[b]
Lifetime alcohol intake, kg	2,067.43 (1,409.63)	2,332.07 (1,516.47)	0.28[b]
Craving for alcohol (OCDS-G score)	12.84 (7.71)	14.17 (7.49)	0.48[b]
Trait impulsivity (BIS-15)	31.87 (6.26)	32.48 (6.20)	0.65[c]
Current anxiety (HADS)	4.42 (3.32)	5.21 (3.65)	0.32[b]
Current depressivity (HADS)	3.57 (3.31)	3.82 (4.18)	0.64[b]

ADS, Alcohol Dependence Scale [42]; BIS-15, Short German version of the Barrat Impulsiveness Scale-15 [43]; CBM, cognitive bias modification; HADS, Hospital Anxiety and Depression Scale [44], scores below 8 were defined as not clinically relevant; OCDS-G, German version of Obsessive Compulsive Drinking Scale [45]. [a] χ^2 test. [b] Wilcoxon rank-sum test. [c] *t* test.

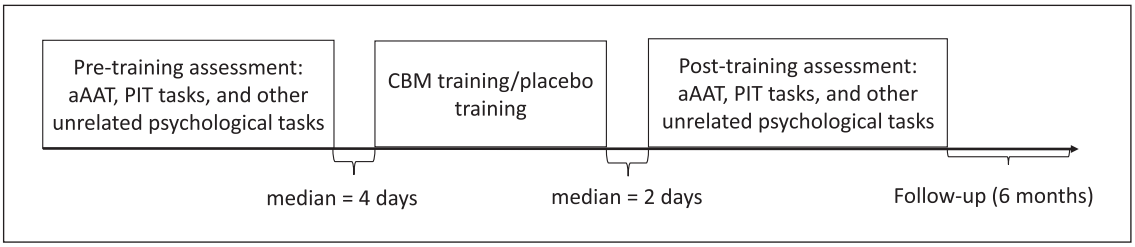

Fig. 2. The timeline of the study procedure. aAAT, alcohol approach/avoidance task; CBM, cognitive bias modification; PIT, Pavlovian-to-instrumental transfer.

as well as between participants who had known relapse outcome (abstinence or relapse) and who did not because of incomplete follow-up information, were reported in online supplementary Material S1, Tables S1 and S2 (for all online suppl. material, see www.karger.com/doi/10.1159/000526805). Patients were offered to attend group sessions in our outpatient department after study participation. The number of patients participating in group session did not differ between the CBM training and the placebo training groups ($n = 27$ in the CBM training group and $n = 18$ in the placebo training group; χ^2 (1, 52) = 0.73, $p = 0.39$).

Alcohol Approach/Avoidance Task

In the aAAT, participants were presented with 21 alcohol and 21 soft drink pictures and responded to pictures by either pulling (approach) or pushing a joystick (avoidance; see Fig. 3). Whether a picture had to be pulled or pushed was indicated by the inclination of the picture (left or right; the correspondence between push/pull responses and left/right inclinations was counterbalanced across subjects). To increase the perception of approach and avoidance, pulling of the joystick enlarged the picture while pushing the joystick minimized the picture (zooming effect). Each picture was presented twice in each orientation, so that each category had to be approached and avoided equally often. This led to a total of 168 experimental trials (presented in random order). To practice the task, these trials were preceded by practice trials with drink-unrelated neutral pictures (26 at pretest and two at posttest).

Cognitive Modification Bias Training

The CBM training is an adapted version of the aAAT. In the CBM training condition, all alcohol pictures were inclined to the direction that required participants to push the joystick, and all soft drink pictures were inclined to the direction that required participants to pull the joystick. In the placebo training condition, the original aAAT was used, in which both alcohol pictures and soft drink pictures had to be pushed and pulled equally often (see above). Each training session started with 26 practice trials with neutral images which were followed by 224 training trials.

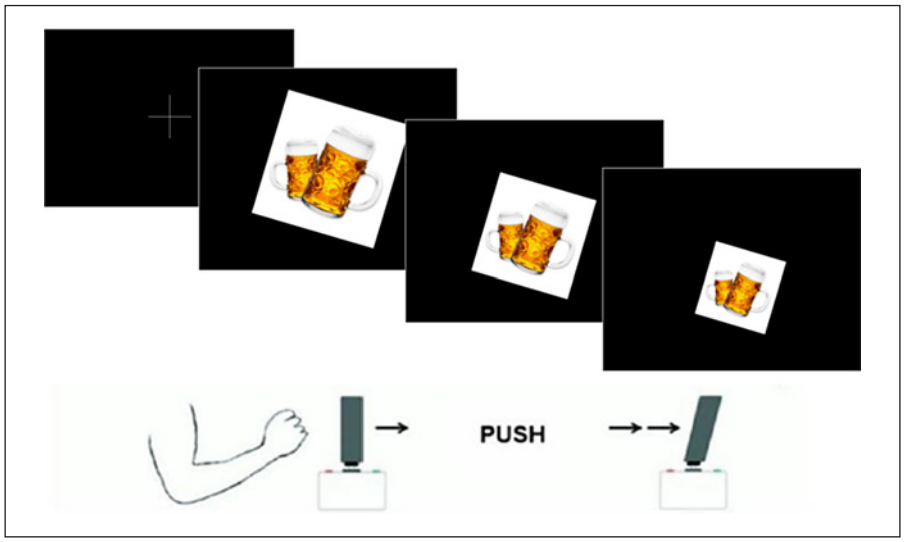

Fig. 3. Alcohol approach/avoidance task (aAAT). An alcohol avoidance trial: an alcohol picture presented on the screen tilted to the right and thus needed to be pushed away. By pushing the joystick, the picture was minimized. Figure adapted from [47].

Pavlovian-to-Instrumental Transfer Paradigm with Non-drug-related Conditioned Stimuli

The non-drug-related PIT paradigm has been described in previous publications [9–11, 48]. The task consisted of four parts (Fig. 4), in which the PIT part was conducted inside a fMRI scanner, while the other parts were conducted outside the scanner. The neuroimaging results will be presented elsewhere. Participants were informed that their performance during all parts (except for Pavlovian training) will affect the bonus they win from the task, which they will receive at the end of the experiment (minimum payout was set to 5 EUR and maximum to 15 EUR).

1. Instrumental training. Participants received probabilistic instrumental training and learned to emit a go or a no-go response for each of six different instrumental shell stimuli (see Fig. 4a). In go trials, collecting a shell by pressing the button repeatedly led to a monetary reward of 0.2 EUR with 80% probability and a loss of 0.2 EUR with 20% probability, and vice versa for not collecting it. In no-go trials, collecting a shell led to monetary loss with 80% probability and reward with 20% probability, and vice versa for not collecting it. Each trial lasted for 2 s. Pressing the button for five or more times led to successful shell collection, while less or no button presses led to no collection. The instrumental training stopped when the participant reached a criterion of 80% correct responses over 16 consecutive trials (for a minimum of 60 trials) or when a maximum of 120 trials were completed.
2. Pavlovian training. In each trial, a compound stimulus (conditioned stimulus, CS) consisting of a fractal picture and a pure tone was paired with an unconditioned stimulus (US: +2 EUR, +1 EUR, 0 EUR, −1 EUR, −2 EUR; negative USs were presented as coins with a superimposed red cross). The US and CS were presented simultaneously for 3 s after a short delay of 0.5 s (delayed conditioning). Participants were instructed to passively watch and memorize the pairings. Five CSs were introduced to pair with five different USs separately. Participants completed 80 trials in this part.
3. PIT. Participants performed the same instrumental task as in the instrumental training part, with CSs that had already been associated with monetary outcomes during Pavlovian conditioning tiling the background. No outcome feedback of each trial was presented in this part, but participants were instructed that their performances would lead to the final monetary outcome. Participants completed 90 PIT trials with Pavlovian CS background.
4. Forced choice task. Finally, participants had to choose one CS over another between two CSs that were presented sequentially and remained on screen for choice. All possible CS pairings were presented 3 times in randomized order. Each choice trial was presented for 2 s. This task was used to verify the effect of Pavlovian training.

Pavlovian-to-Instrumental Transfer Paradigm with Alcohol versus Water Background Cues

We conducted $n = 72$ PIT trials using alcohol versus water cues as background stimuli in the transfer phase. Two pictures of the participant's favorite alcoholic drink (glasses of wheat beer, red wine, white wine, or schnapps) and two pictures of water glasses were used as stimuli; unlike in the non-drug-related PIT task, there was no Pavlovian training phase and we assumed that these cues already act as Pavlovian conditioned stimuli [15]. In the alcohol/water trials, participants performed the instrumental task with one picture of either alcoholic drink or water tiled the background, and the sound of pouring alcohol or water into a glass was played spontaneously. As in the non-drug-related PIT task, participants then performed a forced choice task between beverage stimuli.

Data Analysis

Data were analyzed using R System for Statistical Computing Version 4.0.3 (R Development Core Team 2020). Among the 95 participants who completed the training sessions, three did not take the post-AAT and, therefore, were excluded, and four were discarded because they had an error response rate above 35% in at least one of the aAAT in line with Wiers et al. [19]. A final sample of 88 participants was analyzed to investigate the training effect on aAAT (see Fig. 1). Trials with no or incorrect responses were also discarded. In addition, to exclude extreme response time of trials

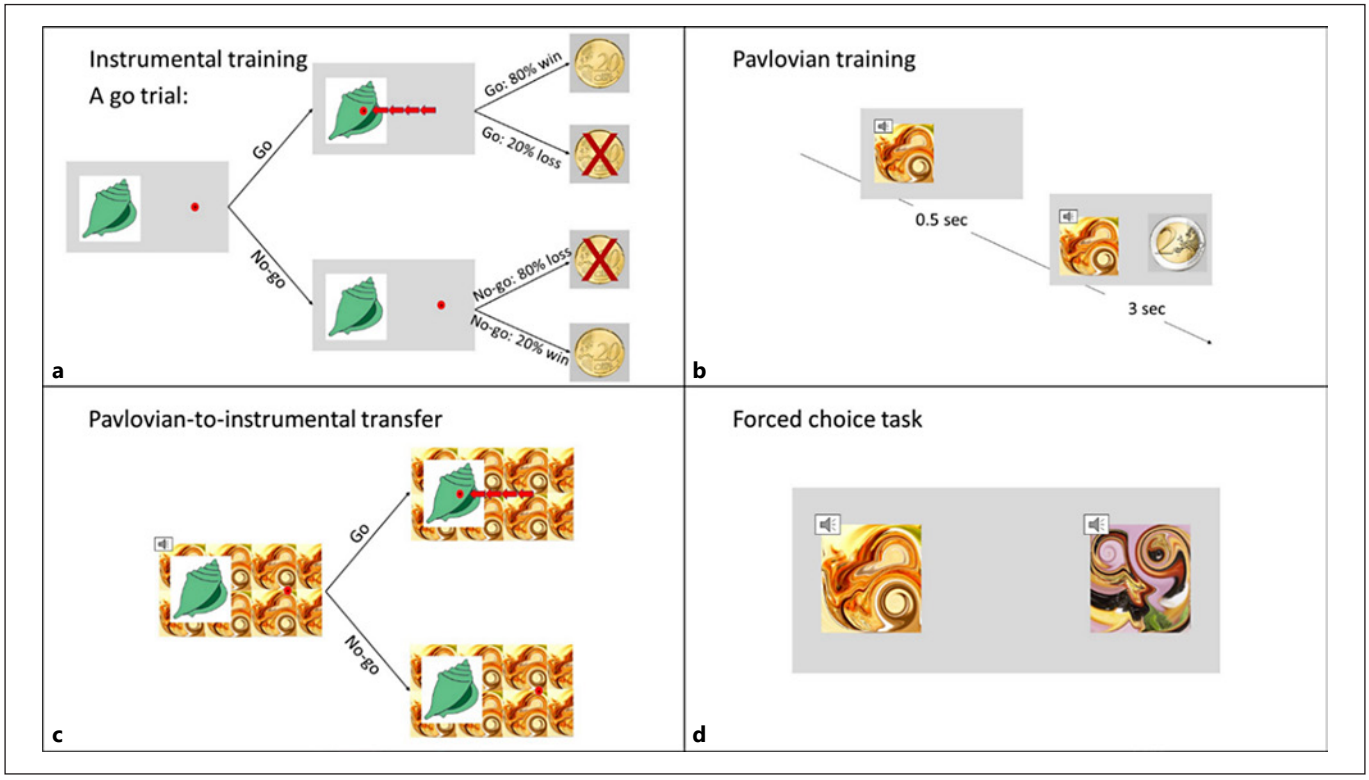

Fig. 4. PIT paradigm. **a** Instrumental training: a go trial is depicted as an example in the figure. By pressing the button for five or more times, the shell would be collected and lead to a reward of 0.2 EUR with 80% probability and loss of 0.2 EUR with 20% probability, and vice versa for not collecting it. The probability of monetary reward/loss after an action of collect/non-collect was the opposite for no-go trials (not depicted here). **b** Pavlovian training: a conditioned stimulus (a fractal picture combined with a pure tone) was paired with a simultaneously presented unconditioned stimulus (e.g., a 2 EUR coin) after a short delay of 0.5 s. **c** PIT: participants performed the instrumental task with a CS tiling the background. **d** Forced choice: two fractal CSs were presented, and participants had to choose the better one.

in our data, the 1% fastest and 1% slowest trials in each aAAT were discarded, which leaves trials with a response time ranging from 350 ms to 3,000 ms to be included in analyses. Following the method used in Wiers et al. [19], a standardized D score was calculated to reflect the approach bias to a stimulus category for each subject. The D score was the median response time difference between pushing pictures of one stimulus category (alcohol or soft drinks) and pulling them divided by an individual's standard deviation of overall response times. We further calculated a score (named D-diff score) to reflect an approach bias to alcohol relatively to soft drink as in some previous studies (e.g., [21, 26, 30]), so that a negative D-diff scores reflects a bias toward approaching soft drinks, and a positive D-diff score indicates a bias toward approaching alcoholic drinks. Specifically, the D scores and D-diff score were calculated as:

- D score$_{(alcohol)}$ = (Push median RT$_{(alcohol)}$ − Pull median RT$_{(alcohol)}$)/personal SD
- D score$_{(soft\ drink)}$ = (Push median RT$_{(soft\ drink)}$ − Pull median RT$_{(soft\ drink)}$)/personal SD
- D-diff score = D score$_{(alcohol)}$ − D score$_{(soft\ drink)}$
- (RT: response time. SD: standard deviation)

A linear mixed-effect model (LMM) (R-package: lme4 [49]) was established to associate the D-diff score with training condition (CBM training and placebo training, coded as +0.5 and −0.5, respectively), time point (pretest and posttest, coded as −0.5 and +0.5, respectively), and their interaction term as regressors. Post hoc multiple comparisons were conducted using the R-package emmeans [50]. To make the analysis comparable to previous studies (e.g., [19, 20]), we also checked the training effect on aAAT with the measurement of D score and reported the results in online supplementary Material S2 and Figure S2.

Regarding the PIT tasks, among all 95 participants who completed the training sessions, 8 subjects did not finish the PIT tasks for both the pretest and the posttest or had incorrect data record due to technical problems and had to be excluded. Besides, 6 patients did not perform the forced choice task above chance, which indicates that they probably did not successfully learn the correlation between CSs and USs. Therefore, these participants were also not included in further analyses. A final sample of 81 participants was available to investigate the training effect on PIT tasks.

For the non-drug-related PIT, a generalized LMM (GLMM) was established to regress the number of button presses in each trial. The value of Pavlovian CS in background (Pavlovian CS val-

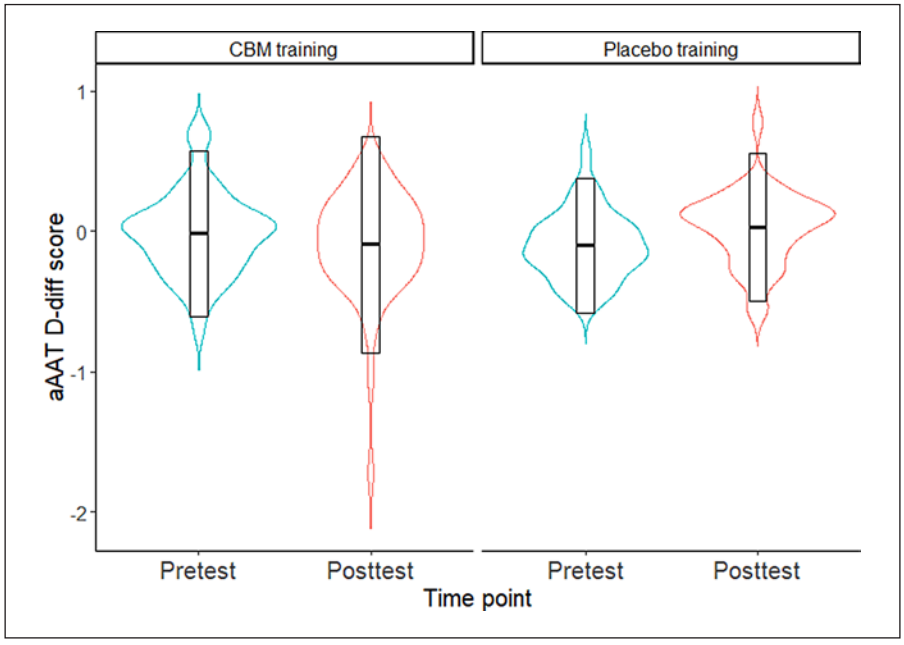

Fig. 5. Participants' alcohol approach bias (i.e., D-diff score) in two training conditions at two time points. The black box with a cross bar represents the mean and standard deviation. aAAT, alcohol approach/avoidance task; CBM, cognitive bias modification.

ue: +2, +1, 0, −1, −2), instrumental condition (go and no-go; coded as +0.5 vs. −0.5, respectively), training condition (CBM training and placebo training; coded as +0.5 vs. −0.5, respectively), and time point (pretest and posttest, coded as −0.5 and +0.5, respectively), as well as the interaction of Pavlovian CS value, training condition and time point were included as regressors. Subject IDs, instrumental stimuli (shells), and Pavlovian CSs (fractal combined with pure tone) were taken as random effects to be controlled. For the drug-related PIT trials, a similar GLMM was conducted with a regressor of beverage type (alcohol and water, coded as +0.5 and −0.5, respectively). A detailed description referring to an unrelated sample can be found in Schad et al. [15]. To further examine if the training effect on PIT differed between instrumental go and no-go trials, we conducted additional GLMMs separately for non-drug-related and drug-related PITs with interaction terms involving instrumental condition in online supplementary Materials S3 and S4, Tables S3 and S4.

Furthermore, based on findings from Wiers et al. [19], we explored future relapse status (relapse vs. abstinence) as a function of training condition using a χ^2 test with both per-protocol and ITT analysis approaches [37]. For per-protocol analysis, patients were defined as relapsers if at least five standard drinks (e.g., one standard drink = 0.33 L beer) for males and at least four standard drinks for females were consumed on one drinking occasion (i.e., heavy drinking) during the follow-up. N = 33 patients relapsed, while n = 24 patients remained abstinent. For ITT analyses, patients who did not respond or had incomplete follow-up interviews were also categorized into the "relapser" group (as in [19, 20]). Another ITT was conducted which additionally included the 10 patients who did not complete the training but took at least one training session before participation withdrawal. In addition to relapse status as the treatment outcome, a Wilcoxon rank-sum test was conducted to explore the training group differences in the number of heavy drinking days during follow-up. Moreover, anxiety and depression scores as covariates of CBM effect on relapse [28] were explored with clinical outcomes of both relapse status and the number of heavy drinking days in online supplementary Material S5. Additionally, we explored whether prospective relapsers and abstainers (with known relapse status) differed in aAAT, non-drug-related PIT and drug-related PIT before or after the training using LMM or GLMM. In the exploratory part of the study, all p values are only given for descriptive reasons.

To eliminate the potentially confounding effect of a longer time-gap between training sessions on the efficacy of CBM, we rerun all the main analyses with a subsample who completed the training sessions within 2 weeks (n = 72) in online supplementary Material S6.

Results

CBM Training on aAAT

The aAAT performances are shown in Figure 5. There was a significant interaction of training condition and time point (estimate = −0.21, t = −2.20, p = 0.03, see Table 2). Despite opposite direction of D-diff score changes in the two conditions (i.e., a decrease tendency of D-diff score in the CBM training group and an increase tendency of D-diff score in the placebo group from the pretest to the posttest) as shown in Figure 5, the post hoc analysis of D-diff score change in neither group yielded significant results (the CBM training group: estimate = −0.08, t = −1.30, p = 0.20; the placebo training group: estimate = 0.13, t = 1.78, p = 0.08). Also, the CBM training group and

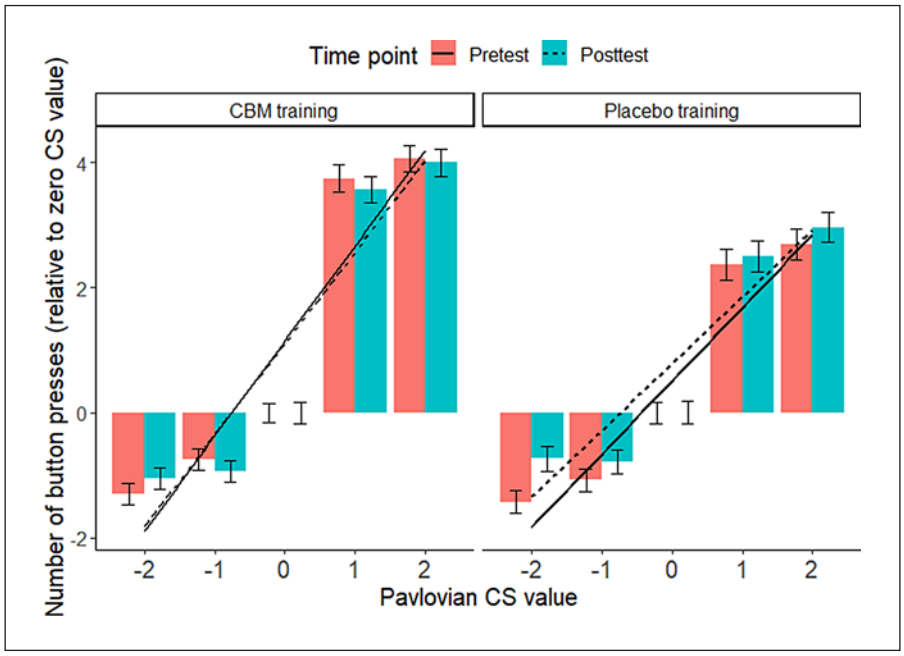

Fig. 6. Non-drug-related Pavlovian-to-instrumental transfer (PIT) effect in two training groups at two time points. CBM, cognitive bias modification; CS, conditioned stimulus shown as tiled background.

Table 2. CBM training effect on aAAT D-diff score

Parameter	Estimate (SE)	*t*	*p* value
Intercept	−0.05 (0.02)	−2.01	0.05
Training condition (CBM training vs. placebo training)	−0.02 (0.05)	−0.38	0.71
Time point (posttest vs. pretest)	0.03 (0.05)	0.57	0.57
Training condition × time point	−0.21 (0.09)	−2.20	0.03

aAAT, alcohol approach/avoidance task; CBM, cognitive bias modification.

the placebo group did not show a significant difference in D-diff scores at either the pretest (estimate = 0.09, $t = 1.24$, $p = 0.22$), or the posttest (estimate = −0.12, $t = -1.79$, $p = 0.08$).

CBM Training on the Non-drug-related PIT

Participants' performances in the instrumental training part and the Pavlovian training part at two time points are reported in online supplementary Materials S7 and S8, respectively. In short, the instrumental learning and the Pavlovian learning performances did not differ between different training conditions or different assessment time points. Regarding PIT performance, patients displayed significant PIT effects across training conditions and time points (i.e., higher number of button presses in trials with higher valued Pavlovian CSs in background; main effect of Pavlovian CS value, estimate = 0.26, $z = 93.46$, $p < 0.001$, see Fig. 6; Table 3). There was no significant interaction between Pavlovian CS value, training condition and time point (estimate = 0.006, $z = 0.55$, $p = 0.58$), which suggests that the changes from the pretest to the posttest did not differ significantly between the two training conditions (change in the CBM training group: estimate = −0.04, $z = -5.41$, $p < 0.001$; in the placebo group: estimate = −0.04, $z = -5.01$, $p < 0.001$). Besides, contrary to our expectation, the PIT effect was larger in the CBM training group compared to the placebo group before the training (estimate = 0.06, $z = 7.05$, $p < 0.001$). Since participants were randomly assigned to different training conditions, such a difference should be coincidental. The group difference in the PIT effect lasted to the posttest (estimate = 0.06, $z = 8.17$, $p < 0.001$).

CBM Training on the Drug-related PIT

Similar to our previous findings with the drug-related PIT [15, 48], alcohol background stimuli inhibited the ap-

Table 3. CBM training effect on the non-drug-related PIT

Parameter	Estimate (SE)	*Z*	*p* value
Intercept	1.47 (0.05)	28.53	<0.001
Pavlovian CS value	0.26 (0.00)	93.46	<0.001
Instrumental condition (go vs. no-go)	0.72 (0.06)	12.03	<0.001
Time point (posttest vs. pretest)	0.02 (0.01)	1.86	0.06
Training condition (CBM training vs. placebo training)	0.05 (0.07)	0.63	0.53
Pavlovian CS value × time point	−0.04 (0.01)	−7.27	<0.001
Instrumental condition × time point	0.38 (0.02)	23.68	<0.001
Pavlovian CS value × training condition	0.06 (0.01)	10.74	<0.001
Instrumental condition × training condition	−0.05 (0.02)	−2.85	0.004
Time point × training condition	0.07 (0.02)	4.03	<0.001
Pavlovian CS value × time point × training condition	0.006 (0.01)	0.55	0.58
Instrumental condition × time point × training condition	−0.30 (0.03)	−9.46	<0.001

CBM, cognitive bias modification; CS, conditioned stimulus shown as tiled background; PIT, Pavlovian-to-instrumental transfer.

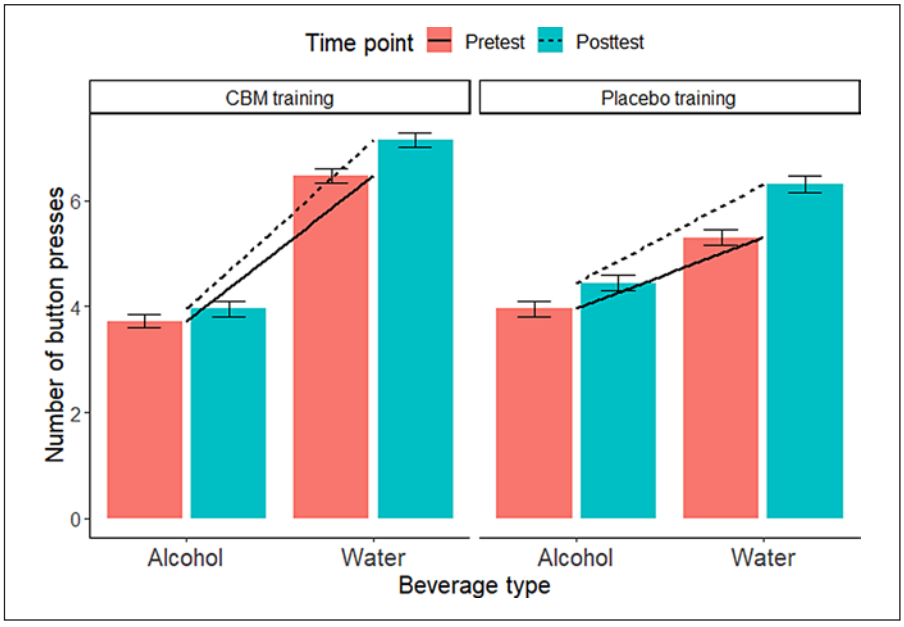

Fig. 7. Drug-related Pavlovian-to-instrumental transfer (PIT) effect in two training groups at two time points. CBM, cognitive bias modification.

proach behavior as compared to the water background stimuli in AD patients (main effect of beverage type: estimate = −0.45, z = −52.02, p < 0.001). There was no significant interaction between beverage type, training condition and time point (estimate = 0.02, z = 0.58, p = 0.56; see Fig. 7; Table 4), which indicates no training effect on the drug-related PIT. The exploratory post hoc analysis showed no significant change of the drug-related PIT effect from the pretest to the posttest in either the CBM training group (estimate = −0.04, z = −1.77, p = 0.29) or the placebo training group (estimate = −0.06, z = −2.17, p = 0.13). Moreover, the inhibition effect of alcohol cues relative to water cues was stronger in the CBM training group compared to the placebo group at both the pretest (estimate = −0.26, z = −10.48, p < 0.001) and the posttest (estimate = −0.24, z = 10.25, p < 0.001).

Clinical Outcomes

Patients' relapse status did not significantly differ between the two training groups (per-protocol analysis with 57 patients who completed the training and with known relapse status: χ^2 (1, 57) = 1.22, p = 0.27; ITT analysis with 95 patients who completed the training and those with incomplete follow-up information categorized as relaps-

Table 4. CBM training effect on the drug-related PIT

Parameter	Estimate (SE)	*Z*	*p* value
Intercept	1.47 (0.06)	26.45	<0.001
Beverage type (alcohol vs. water)	−0.45 (0.01)	−52.02	<0.001
Instrumental condition (go vs. no-go)	0.81 (0.07)	11.27	<0.001
Time point (posttest vs. pretest)	0.03 (0.01)	3.23	0.001
Training condition (CBM training vs. placebo training)	0.06 (0.08)	0.74	0.46
Beverage type × time point	−0.05 (0.02)	−2.80	0.005
Instrumental condition × time point	0.42 (0.02)	22.85	<0.001
Beverage type × training condition	−0.25 (0.02)	−14.66	<0.001
Instrumental condition × training condition	−0.10 (0.02)	−5.69	<0.001
Time point × training condition	0.02 (0.02)	1.32	0.19
Beverage type × time point × training condition	0.02 (0.03)	0.58	0.56
Instrumental condition × time point × training condition	−0.43 (0.04)	−11.65	<0.001

CBM, cognitive bias modification; PIT, Pavlovian-to-instrumental transfer.

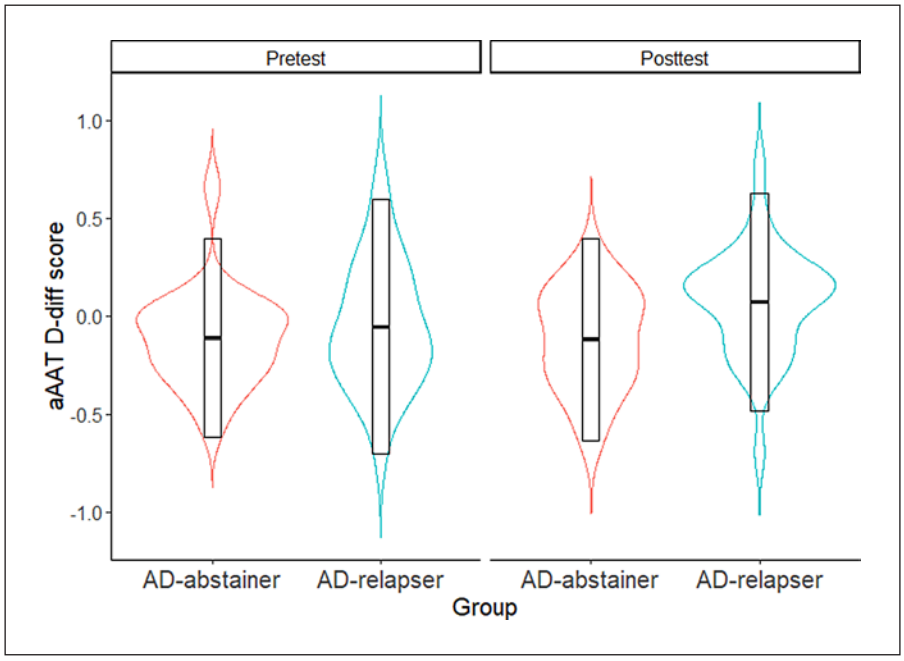

Fig. 8. Prospective relapsers showed higher alcohol approach bias (i.e., D-diff score) compared to prospective abstainers at the posttest. aAAT, alcohol approach/avoidance task.

ers: χ^2 (1, 95) = 1.92, p = 0.17; ITT analysis with 105 patients who took at least one training session and those with incomplete follow-up information categorized as relapsers: χ^2 (1, 105) = 1.36, p = 0.24). The number of heavy drinking days in the 6-month follow-up also did not differ between two training groups (w = 176.5, p = 0.34; Wilcoxon rank-sum test). These results do not support an effect of CBM on future relapse risk.

We explored if the alcohol approach bias or the two PIT effects correlate with future relapse status. Regarding the aAAT, there was no significant interaction of relapse status and time point on the aAAT D-diff score (estimate = 0.13, t = 1.18, p = 0.24) but a descriptively significant main effect of relapse group (estimate = 0.12, t = 2.23, p = 0.03). We conducted exploratory post hoc group comparisons, and observed that future relapsers displayed a stronger alcohol approach bias at posttest but not at pretest compared to abstainers (posttest: estimate = 0.19, t = 2.41, p = 0.02; pretest: estimate = 0.06, t = 0.74, p = 0.46; shown in Fig. 8).

Regarding the non-drug-related PIT, we observed a significant interaction of Pavlovian CS value, time point

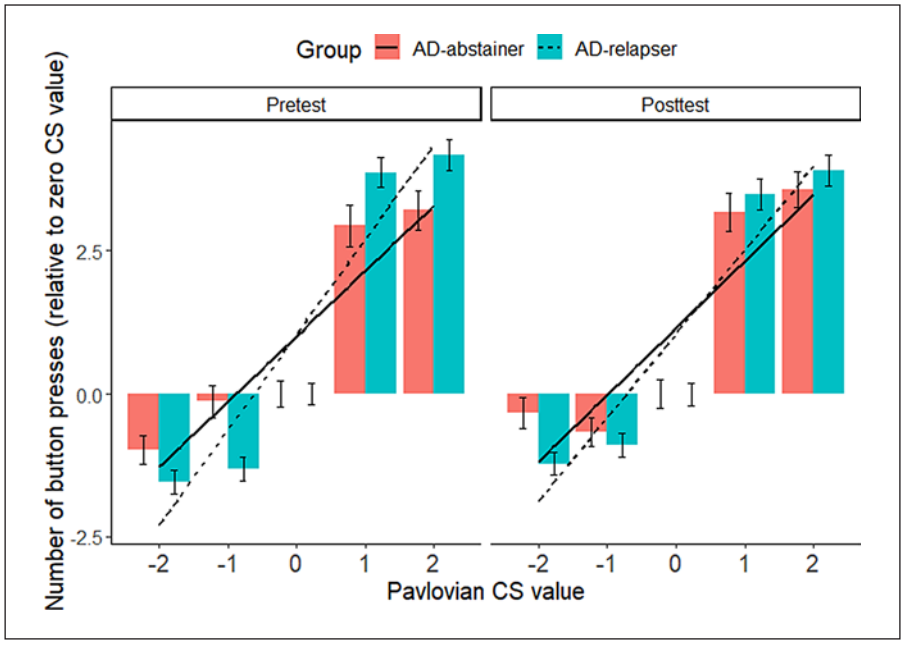

Fig. 9. Prospective relapsers showed higher non-drug-related Pavlovian-to-instrumental transfer (PIT) effect compared to prospective abstainers at both the pretest and the posttest. CS, conditioned stimulus shown as tiled background.

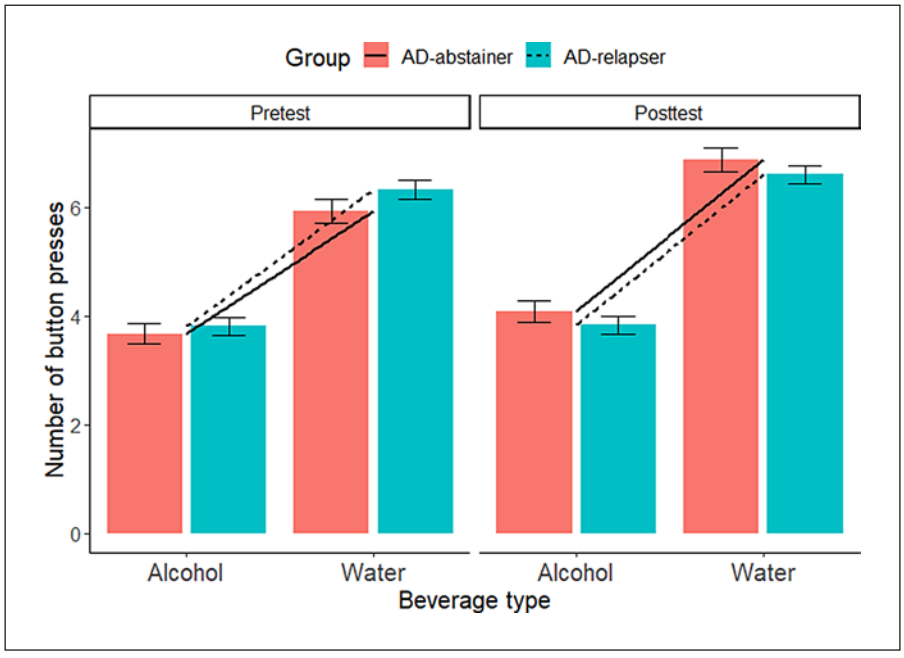

Fig. 10. Prospective relapsers and abstainers did not differ in the drug-related Pavlovian-to-instrumental transfer (PIT) effect at either the pretest or the posttest.

and relapse group (estimate = −0.05, $z = -3.92$, $p < 0.001$). Post hoc analysis showed that PIT effects at both the pretest and the posttest were higher in relapsers compared to abstainers (pretest: estimate = 0.12, $z = 12.28$, $p < 0.001$; posttest: estimate = 0.07, $z = 6.91$, $p < 0.001$; see Fig. 9). PIT effect decreased from the pretest to the posttest in future relapsers (estimate = −0.063, $z = -6.95$, $p < 0.001$) but not in abstainers (estimate = −0.009, $z = -0.87$, $p = 0.39$).

With regard to the drug-related PIT task, we observed no significant interaction of beverage type, time point and relapse group (estimate = 0.002, $z = 0.04$, $p = 0.97$). Exploratory post hoc group comparisons showed no difference between future relapsers and abstainers in drug-related PIT at either the pretest or the posttest (pretest: estimate = −0.03, $z = -0.86$, $p = 0.83$; posttest: estimate = −0.03, $z = -0.84$, $p = 0.83$; see Fig. 10).

Discussion

The current study examined whether CBM training can interact with non-drug-related or drug-related PIT effects in AD patients that has previously been associated with treatment outcome [9, 11, 15]. We exploratively replicated the previous observation in an unrelated sample that the non-drug-related PIT effect was stronger in prospective relapsers versus abstainers [11]. We observed a decreased non-drug-related PIT effect following detoxification in both groups. However, the magnitude of this PIT effect changed over time did not differ significantly between the CBM training group and the placebo training group, which does not support an effect of CBM on PIT performance as assessed in this study. Regarding the drug-related PIT, we did not replicate our previous finding that behavioral inhibition elicited by background alcohol versus water cues is associated with a better treatment outcome [15], and there was no significant change in drug-related PIT effect over time. With respect to the alcohol approach bias assessed by aAAT, a stronger approach bias after training was associated with an increased relapse risk, thus confirming similar observations in AD patients [51] (but see [52, 53]).

We replicated previous findings [11], which showed that an increased non-drug-related PIT effect predicts relapse in AD patients, while we did not replicate the previous finding regarding relapse prediction by a drug-related PIT effect [15]. In our current study, the strength of the non-drug-related PIT effect decreased with time, which may be because patients were more familiar with the PIT task at the posttest and thus were less distracted by the task-irrelevant Pavlovian CSs. Decisively, we did not observe a significant effect of CBM training on the non-drug-related or drug-related PIT effects. These null findings suggest that contrary to our hypothesis, CBM may not interact with mechanisms assessed by our non-drug-related or drug-related PIT paradigms [9, 11, 15].

Our observation that CBM training did not interact with the drug-related PIT effect maybe partly due to the already existing inhibition effect by alcohol stimuli on instrumental approach behavior compared to water stimuli at the pretest, which resulted in a rather small room to further enhance the suppression effect of alcohol stimuli following CBM training. In our drug-related PIT paradigm, the value of alcohol stimuli was not established through laboratory Pavlovian conditioning, therefore could be influenced by the effect of detoxification or individuals' goal to remain abstinent [15]. During detoxification, a negative implicit association could be established between alcohol-related thoughts and aversive subjective craving [54]. In addition, a conscious goal to remain abstinent may also play a role in the aversive features of alcohol stimuli [15]. Patients in our study conducted the pretest assessment within a relatively short time period after detoxification (median = 21 days), when they may have a generally strong motivation to remain abstinent from alcohol, which may explain the aversively valued alcohol stimuli. Besides, our drug-related PIT task only measured the general PIT effect that reflects unspecific arousal but not the specific PIT effect (that assesses on the retrieval of particular actions based on their outcome) [3]. Whether CBM effects on automatic approach tendencies interact with outcome-specific PIT effect elicited by alcohol background cues can be investigated in future studies.

An effect of CBM training on results of the non-drug-related PIT task would require substantial generalization of such training effects on general approach and avoidance behavior. Previous research regarding the generalization of CBM effects was mainly limited to drug-related tasks and yield mixed findings. While two studies found significant CBM effects on reducing alcohol approach associations as assessed by the implicit association task [19, 32], other studies did not find such a significant effect [55–57]. Besides, one study reported no generalization effect of CBM to selective attention to alcohol cues [58]. It is worthy to note that the three studies which observed no generalization to implicit association task also did not find a CBM effect on the alcohol approach bias in non-clinical drinkers [55–57]. Since CBM may work best in persons with more severe alcohol use disorder [31], we assessed detoxified patients with alcohol dependence but nevertheless observed no significant effect of CBM on our PIT tasks. The null training effect on the non-drug-related PIT effect may partly be due to the inability of our non-drug-related PIT task to disentangle general versus specific PIT effects, as monetary reward was used for both the Pavlovian conditioning and the instrumental task but with different values. The effect of Pavlovian CSs in our task could be contributed by both specific and general PIT processes [48]. Future studies could assess whether CBM interact only with general or outcome-specific PIT effects with non-drug-related stimuli.

It has been suggested that CBM training works via the change of alcohol approach bias [20, 31, 58, 59]. We may not have observed an effect of CBM on the strength of any PIT effect because there was no significant effect of our CBM training on the alcohol approach bias as assessed with the aAAT. In our study, a significant training condi-

tion and assessment time point interaction indicates differential aAAT performance changes between the CBM training group and the placebo training group, however, the decrease of the alcohol approach bias (as indicated by the D-diff score) did not reach significance in the CBM training group. The null effect of CBM training on the alcohol approach bias may (at least partly) be explained by the lack of an alcohol approach bias before the training in our patient cohort (D-diff score: mean = −0.05, SD = 0.28, t (87) = −1.82, p = 0.07), which is not in line with findings in some previous studies [18–20]. The alcohol approach bias was observed in patients during inpatient withdrawal treatments [24, 60]. However, when considering other measurements such as stimulus-response compatibility (SRC) task, several previous studies reported no approach bias or even an avoidance bias to alcohol stimuli in AD patients (compared to controls) after detoxification [52, 61, 62]. These inconsistent findings may be explained by differences in assessment tasks, how the approach bias was calculated, or may be due to differences in sample characteristics, including patients' drinking status and treatment seeking motivation [63]. The lack of a significant alcohol approach bias in our study could thus have led to a floor effect that prevents CBM training to further reduce already minimal or even absent alcohol approach.

The alcohol approach bias was stronger in relapsers compared to abstainers as shown in the exploratory analysis results, which indicates a predictive role of alcohol approach bias in future relapse. Further exploratory post hoc analysis found that the association between aAAT D-diff score and relapse status was mainly driven by the posttest rather than the pretest. This suggests that the alcohol approach bias could be dynamic [64], and future research to examine the association between the alcohol approach bias and relapse should take the assessment time into consideration.

With respect to our exploratory assessment of CBM training on future relapse risk, we failed to observe a significant effect. Previous research of CBM intervention targeting on the alcohol approach bias and treatment outcome also showed discrepant results [59, 65, 66]. Although several studies reported prominent effect of CBM on reducing the alcohol approach bias and decreasing future relapse risk or drinking behavior [19, 20, 23, 24, 27], there are also studies did not find similar effects on drinking behavior [22]. Wiers et al. [22] discussed the controversial findings, and pointed out several factors that could influence the CBM intervention efficacy, including the types of study (experimental study or clinical trial) and the settings (clinical or online) [59]. It should also be noted that two clinical studies that reported prominent CBM effect did not use CBM intervention as the only but as an add-on intervention to cognitive behavior therapy to AD patients [19, 20]. Study with problem drinkers also did not support CBM effect on reducing drinking compared to placebo training [22]. In accordance with that study, a recent systematic review suggested that severity of alcohol use disorder may be associated with treatment responses, with only severely affected patients showing a positive effect of CBM [31]. However, our patients all fulfilled criteria for alcohol dependence, suggesting that severity of alcohol dependence may not explain our null finding. Instead, the above discussed floor effects regarding alcohol approach during early abstinence may help to explain why CBM did not significantly affect treatment outcomes in our study. Also, our study had a limited sample size that was powered to detect whether behavioral PIT effects are modified by CBM training but not powered to detect a significant effect of CBM training on relapse, which previously required much larger sample sizes [19, 20, 24, 27]. Our study may lack the statistical power to detect an effect of CBM on relapse status.

In conclusion, we observed that an increased non-drug-related PIT effect predicted future relapse in AD patients similar to the previous findings [11], and an increased alcohol approach bias after CBM training was also associated with a poor treatment outcome [51]. However, we observed no effects of CBM training, neither on the alcohol approach bias nor the drug-related or non-drug-related PIT effects. Also, there was no evidence supporting CBM training effect on the relapse risk in the follow-up period of 6 months. These null findings may be due to specific sample characteristics [18], our limited sample size or further unknown factors. Given the originally very promising [19, 20] but recently mixed results regarding CBM in the treatment of patients with alcohol dependence [31, 65], further studies are needed to better target the mechanism, mediators, and moderators of CBM interventions in alcohol dependence.

Statement of Ethics

This study protocol was reviewed and approved by the local ethics committees of Charité Universitätsmedizin Berlin (approval number: EA1/268/14) and Technische Universität Dresden (approval number: EK 300082014). All participants gave written informed consent prior to participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Andreas Heinz was responsible for the study concept and design. Ulrich Zimmermann, Maria Garbusow, and Miriam Sebold contributed to the execution of the study protocols and data collection. Ke Chen performed the statistical analyses and wrote the first draft of the manuscript. Andreas Heinz, Ulrich Zimmermann, Maria Garbusow, Miriam Sebold, and Hilmar G. Zech provided a critical revision of the manuscript for important intellectual content. All the authors (Ke Chen, Maria Garbusow, Miriam Sebold, Hilmar G. Zech, Ulrich Zimmermann, and Andreas Heinz) critically reviewed the content and approved the final version for publication.

Data Availability Statement

The data that support the findings of this study are available at https://osf.io/hgva2/.

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