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RESEARCH ARTICLE

Does selective inhibition training reduce relapse rates when added to standard treatment of alcohol use disorder? A randomized controlled trial

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Abstract

Background: Alcohol-dependent individuals tend to selectively approach alcohol cues in the environment, demonstrating an alcohol approach bias. Because approach bias modification (ApBM) training can reduce the approach bias and decrease relapse rates in alcohol-dependent patients when added to abstinence-focused treatment, it has become a part of regular treatment. Moreover, in selective inhibition (SI) training, responses to one category of stimuli (i.e., alcohol stimuli) are selectively inhibited in an adapted Go/No-Go task. SI-Training has been found to effectively devalue the inhibited category and to reduce consumption of alcohol among social drinkers. This study investigated whether SI-Training can further improve the effects of treatment as usual that includes ApBM, and if so, whether the effect is mediated by a devaluation of the inhibited alcohol stimuli.

Methods: Abstinent alcohol-dependent inpatients (N=434) were randomly assigned to receive 6 sessions of either active (n = 214, 32% female) or sham (n = 220, 38% female) SI-Training, in addition to standard treatment that includes active ApBM. Ratings were used to assess changes in the evaluation of alcohol stimuli after the training. Relapse rates were assessed 3 and 12 months after treatment discharge.

Results: Alcohol stimuli were rated negatively before and after the training, and the training did not influence these ratings. Evaluation of nonalcoholic drinks became more positive after active SI-Training. Both ApBM and SI-Training showed the expected training effects on reaction times. Contrary to expectations, SI-Training conditions did not yield different abstinence rates 3 or 12 months after treatment.

Conclusions: We found no evidence supporting the hypothesis that SI-Training amplifies the relapse-preventing effect of ApBM. Moreover, alcohol stimuli were rated negatively before and after treatment and were not influenced by SI-Training.

KEYWORDS
alcohol approach bias, cognitive bias modification, evaluation, relapse prevention, selective inhibition training

INTRODUCTION

Alcohol use disorder (AUD) ranks among the most prevalent psychiatric disorders globally (World Health Organization [WHO], 2018), with high mortality rates (Schwarzinger et al., 2017), considerable disability and tremendous societal costs (Carvalho et al., 2019). Furthermore, despite continuous efforts to improve treatment of this disorder, relapse rates typically exceed 50% in the first year after treatment (e.g., Cutler & Fishbain, 2005).

As AUD develops, cue-elicited action tendencies become more important in determining behavior. The processing of incoming information, and consequently, the behavioral tendencies become biased toward addictive substances (Bechara, 2005; Stacy & Wiers, 2010; Verdejo-Garcia & Albein-Urios, 2021). This leads to an imbalance between strong impulsive reactions toward drug-related cues, along with relatively weak control over these impulses (Bechara, 2005; Wiers et al., 2007). The influence of biased cognitive processes on the maintenance of mental disorders, including addictions, is highlighted by cognitive models (MacLeod & Mathews, 2012; Wiers et al., 2013). To reduce the detrimental influences of cognitive biases on mental health, a new form of translational intervention was developed, collectively called cognitive bias modification (CBM; Wiers et al., 2013). Over the past decade, varieties of cognitive training, all using the principles of CBM, have effectively reduced relapse rates after 1 year by approximately 10% (Eberl et al., 2013; Salemink et al., 2021; Wiers et al., 2011).

To modify cognitive biases in AUD, different types of CBM have been developed. Most evidence for the clinical effectiveness of CBM in AUD has been found for the modification of the tendency to selectively approach alcohol-related stimuli. This approach bias modification (ApBM) in addition to regular inpatient treatment for AUD was repeatedly found to reduce relapse rates of abstinent alcohol-dependent patients 1 year after treatment (Eberl et al., 2013, 2014; Rinck et al., 2018; Salemink et al., 2021; Wiers et al., 2011) as well as when performed during inpatient alcohol detoxification (Manning et al., 2016, 2021). Given the consistent positive effects of ApBM in clinical contexts (Kakoschke et al., 2017a; Wiers, 2018), it has now been included in the clinical treatment guidelines for AUD in Germany (Kiefer et al., 2022; Mann et al., 2016) and Australia (Haber et al., 2021).

Another form of CBM, called selective inhibition training (SI-Training) targets impulsive reactions toward a specific type of cues (alcohol in AUD, or food in obesity, see Stice et al., 2016). In AUD, consumption is stimulated by strong impulsive reactions to drug-related cues (Robinson & Berridge, 2008), including automatically activated approach tendencies toward alcohol cues, together with limited control to counteract such tendencies (Bechara, 2005; Wiers et al., 2013). Although the presence of strong impulsive reactions to alcohol cues is well-known in AUD (Robinson & Berridge, 2008), SI-Training has so far only been tested in heavy drinkers (Bowley et al., 2013; Di Lemma & Field, 2017; Houben et al., 2011, 2012; Jones & Field, 2013). In SI-Training, an adapted Go/No-Go task is used (e.g., Veling et al., 2008). Visual or auditory cues are presented in close temporal and spatial proximity to target pictures (e.g., of alcoholic or nonalcoholic drinks). The cues instruct participants to either execute a motor response by pressing a button (i.e., Go response) or to refrain from responding (i.e., No-Go response). Go cues are sometimes more frequent than No-Go cues, making it difficult to inhibit the regular response occasionally. In the active training condition, pictures of one category (e.g., alcoholic beverages) are always paired with No-Go cues (No-Go pictures) and pictures of another category (e.g., nonalcoholic beverages) are always paired with Go cues (Go pictures). A robust finding in this preclinical literature is that the evaluation of the No-Go pictures becomes less positive from pre- to posttraining, compared to both the Go pictures and pictures not presented during the training. This may then transfer to changes in choice behavior (devaluation effect; see Chen et al., 2016; Johannes et al., 2021).

According to one explanation (Veling et al., 2008), the devaluation occurs because of a response conflict between the approach tendency toward the stimulus and the required response inhibition, which is accompanied by negative affect, which in turn becomes associated with the stimulus (for alternative explanations, see Johannes et al., 2021). Indeed, it was found that pairing alcohol pictures with No-Go cues lowered their positive evaluations and reduced short-term consumption in heavy-drinking individuals (Bowley et al., 2013; Houben et al., 2011, 2012; Jones & Field, 2013).

The effects of SI-Training as an add-on to regular treatment for AUD with the aim to reduce relapse rates after treatment have yet to be examined, particularly when SI-Training is used as an amplifier for other CBM treatments like ApBM. ApBM aims to reduce the alcohol approach tendency toward alcohol stimuli by training avoidance responses. This approach tendency has been reinforced by the rewarding experience of consumption and elicited by exposure to alcohol stimuli. Devaluation of alcohol stimuli by SI-Training might augment the relapse-preventing effect of ApBM. Although it is not yet clear how AUD patients evaluate alcohol, there is some preliminary evidence that AUD patients, compared to social drinkers, have relatively weaker negative associations with alcohol, while having equally positive alcohol associations (Dickson et al., 2013). Hence, making alcohol stimuli even more negative via SI-Training might enhance the relapse-preventing effects of ApBM.

As far as we know, the present study is the first to investigate whether the relapse-preventing effects of inpatient treatment for AUD including ApBM can be amplified by adding SI-Training. Active SI-Training, compared to sham training, was intended to reduce the evaluation of alcohol in abstinent alcohol-dependent patients. Therefore, patients were randomly assigned to receive six sessions of either active or sham SI-Training, along with their regular treatment which included active ApBM. The latter used the same setup as in active conditions of previous studies on ApBM (Eberl et al., 2013, 2014; Rinck et al., 2018; Wiers et al., 2011). SI-Training was based on the studies by Veling et al. (2008) and Chen et al. (2016, 2018). Changes in evaluation of alcohol stimuli were assessed using a rating procedure employed in previous studies (e.g., Chen et al., 2018; Veling et al., 2017). In the following, we will use the terms "active

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training" for the active SI-Training added to active ApBM and "sham training" for the sham SI-Training added to active ApBM because all patients received active ApBM as part of standard treatment. Primary outcome variables were the clinical outcomes at 3-month and 1-year follow-ups (success or not, as in earlier studies) and devaluation of alcohol cues after the SI-Training. We expected that active SI-Training would yield higher success rates than sham SI-Training at both follow-up time points. Further, we expected that active SI-Training would cause a stronger devaluation of alcohol pictures than sham SI-Training, and we explored if it would also reduce the approach bias for alcohol more strongly.

MATERIALS AND METHODS

Participants

Participants were 434 currently abstinent alcohol-dependent patients admitted to a 3-month inpatient treatment at the Salus Clinic Lindow, Germany. Previous studies have repeatedly shown a small effect of alcohol-ApBM, with a reduction in relapse rates by approximately 10% 1 year later (Eberl et al., 2013; Wiers et al., 2011). Therefore, a small add-on effect was assumed here, too. The current sample size yielded power of $1-\beta = 0.83$ with $p = 0.05$ for the detection of a small effect ($w = 0.14$) on relapse rates, in the comparison of active versus sham SI-Training (Faul et al., 2007). With the current sample size, a 10% difference in the relapse rates would be statistically significant. Before signing informed consent, patients were informed about the study and their right to withdraw from it without incurring any disadvantages regarding their treatment. The study was approved by the Ethics Committee of the "Medizinische Hochschule Brandenburg" (E-01-20180326) and the German Pension Fund (10-R-35.08.39.000). This clinical trial was registered with the German Clinical Trial Registry (ID: DRKS00013228). We included every patient with a primary alcohol dependence diagnosis (F10.2 in ICD-10; WHO, 1992), as assessed during the standard intake procedure of the clinic. Exclusion criteria were insufficient command of German, neurocognitive health problems, and the use of anti-craving drugs. Figure 1 shows a CONSORT diagram of the participant flow. The two groups did not differ in gender distribution, age, education level, severity and duration of alcohol dependence, nicotine dependence, depression, or mental burden (Table 1). The two groups of the per-protocol sample ($n = 321$) did not differ on these demographic characteristics either (Table 2).

Procedure overview

During the first 4 weeks of treatment, included patients started with the combined alcohol-ApBM–SI-Training. They were randomly assigned to one of the two experimental conditions as described below. The patients, their therapists, and the interns who assisted during data collection were blind to the fact that one of the training conditions was intended to be active and the other one intended to be a sham condition. For both conditions, the patients received a plausible rationale. Patients may have recognized their training condition, but, just like therapists and interns, were kept blind to the nature of the two conditions. Assigned patients were scheduled to complete six sessions of the combined alcohol-ApBM–SI-Training within the next 2 weeks (each session taking approximately 20 min). Within each training session, patients first completed the alcohol-ApBM, followed by the randomly assigned condition of the SI-Training. In addition to training, all patients followed abstinence-oriented cognitive behavioral therapy, including both individual and group therapy. Before the first and after the sixth training session, all patients rated the drink stimuli used in the ApBM and the SI-Training (taking approximately 10 min). Three months and 1 year after discharge from treatment, participants received a standard follow-up questionnaire. In the questionnaire, they were asked whether they had continuously been abstinent during the past 3 and 12 months, respectively. If this was not the case, they were asked additional questions regarding the type of used drugs, the number and duration of relapse(s), and the way they ended the last relapse. At both time points, patients who did not return the questionnaire were reminded twice by post, and, if they did not answer, a final attempt was made to reach them by phone. If patients were contacted by phone, this was done by therapists or interns who did not know whether the patient had participated in the study, or which training they had received. Using this procedure, a total of 300 (69.1%) patients could be reached after 3 months, and 317 (73.0%) patients after 1 year. Trainings started in December 2017 and were concluded in April 2020. Follow-up measurements lasted until June 2021.

Assessment and outcome measures

At intake, all patients were interviewed using 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." Both the CIDI and the clinical interview were conducted by clinical psychologists and formed the basis for the diagnoses. The German versions of the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), the Beck Depression Inventory (BDI; Hautzinger et al., 1994), and the Symptom Checklist 90-R (SCL-90; Franke & Stacker, 1995) were also administered during intake. Computerized tasks included the alcohol-ApBM, the SI-Training, and pretraining and posttraining assessments of the evaluation of the drink stimuli. The main outcome variables of this clinical randomized controlled trial (RCT) were the treatment success rates at follow-ups after 1 month and 1 year. These were assessed as binary outcome variables (successful outcome or not), using conservative intention-to-treat (ITT) principles. Following the DGSS-4 guidelines as defined by the German Addiction Society (i.e., Deutsche Gesellschaft für Suchtforschung und Suchttherapie, DGSS), successful outcome consisted of either

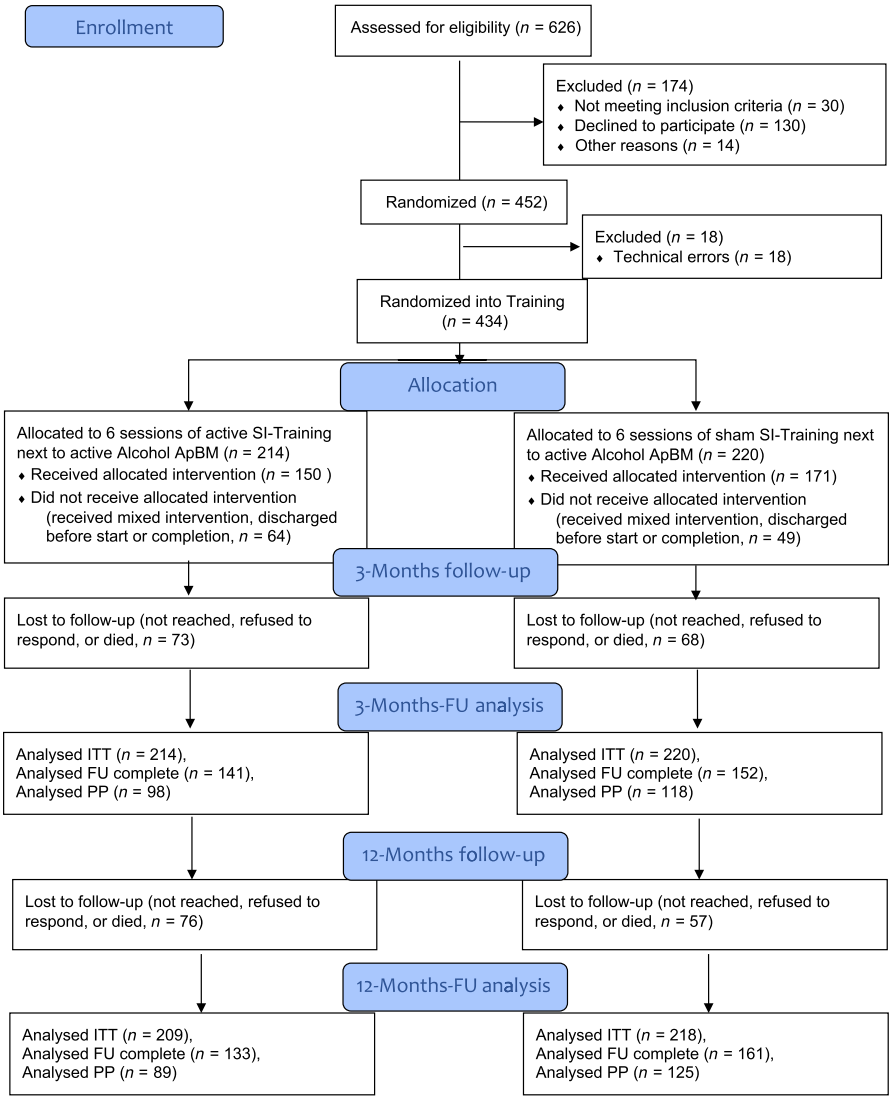

FIGURE 1 CONSORT diagram. The sample sizes shown here relate to analyses of the primary outcome variables "Success at 3-month and 1-year FU." ITT is the intention-to-treat analysis using DGSS4 rules (includes all 434 correctly randomized patients). "FU complete" analysis is according to DGSS1 (includes the 293 patients supplying information at follow-up after 3 months, and the 294 patients supplying information at 1-year follow-up). "PP" analysis is per protocol (includes only the 216 patients who completed the training and supplied information at follow-up after 3 months, and similarly, the 216 patients at 1-year follow-up).

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 before the follow-up assessment. Failure was defined as relapse, death, no contact, or refusal to provide information.

Furthermore, we also assessed treatment success according to the DGSS-1 guidelines defined by the German Addiction Society. DGSS-1 differs from DGSS-4, in that it includes information on treatment outcomes only from patients who could be reached at follow-up and provided information. For DGSS-1, successful outcome 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 before the follow-up assessment. Failure was defined as relapse, as assessed at the follow-up assessment. Finally, we computed per-protocol analyses which included only those patients who provided information about treatment outcomes (as in DGSS-1) and who completed SI-Training.

Questionnaires

Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT (Saunders et al., 1993) is a standard screening instrument for problematic alcohol consumption, assessing drinking amount, frequency, and negative consequences. The AUDIT has a high test–retest reliability (Reinert & Allen, 2007).

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TABLE 1 Mean characteristics of the ITT sample: means (SDs), significance of group differences, and success rates at 3-month and 1-year follow-ups (success includes abstinence and lapse).

Characteristics	All patients ($N = 434$)	Active SI-Training ($n = 214$)	Sham SI-Training ($n = 220$)	p Value
Age in years, mean (SD)	46.67 (10.16)	46.67 (10.30)	47.33 (9.96)	0.76
Gender (% female)	35%	32%	38%	0.26
Education level[a], mean (SD)	3.02 (0.91)	3.07 (0.90)	2.97 (0.93)	0.79
Duration of alcohol problems (years), mean (SD)	11.86 (9.32)	11.84 (9.00)	11.87 (9.64)	0.60
Duration of treatment in days, mean (SD)	82.76 (14.96)	83.15 (15.69)	82.40 (14.25)	0.60
Smoking (% with nicotine dependence)	72%	71%	73%	0.90
Beck Depression Inventory, mean (SD)	15.80 (11.65)	16.036 (11.69)	15.27 (11.61)	0.33
SCL-90, mean (SD)	63.59 (12.14)	63.30 (12.62)	63.86 (11.69)	0.30
AUDIT score, mean (SD)	26.07 (7.65)	26.05 (7.68)	26.10 (7.64)	0.95
Percent success at 3-month follow-up (ITT)	49.8%	48.6%	50.9%	0.66
Percent success at 1-year follow-up (ITT)	42.6%	41.1%	44.1%	0.62

Note: Continuous variables were analyzed with two-group ANOVAs, with $F(1, 432)$. Categorical variables were analyzed with chi-square tests (df = 1). For all analyses, p-values were two-tailed, and alpha was set at 0.05. Standard deviations are presented in parentheses.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; SCL-90, Symptom Checklist-90.

[a]Education level was scored on a scale from 1 (primary school) to 5 (finished university).

TABLE 2 Mean characteristics of the per-protocol sample: means (SDs), significance of group differences, and success rates at 3-month and 1-year follow-ups (success includes abstinence and lapse).

Characteristic	All patients ($N = 321$)	Active SI-Training ($n = 150$)	Sham SI-Training ($n = 171$)	p Value
Age (years), mean (SD)	47.17 (10.06)	46.99 (10.20)	47.33 (9.96)	0.76
Gender (% female)	36%	34%	38%	0.46
Education level[a], mean (SD)	3.07 (0.97)	3.16 (0.89)	3.00 (0.92)	0.49
Duration of alcohol problems (years), mean (SD)	11.81 (9.29)	11.42 (8.96)	12.15 (9.59)	0.49
Duration of treatment (days), mean (SD)	82.50 (15.52)	83.14 (16.80)	84.00 (14.33)	0.49
Smoking (% with nicotine dependence)	72%	71%	73%	0.72
Beck Depression Inventory, mean (SD)	15.42 (11.29)	16.00 (11.39)	14.92 (11.21)	0.40
SCL-90, mean (SD)	62.72 (12.23)	62.56 (12.85)	62.85 (11.69)	0.83
AUDIT score, mean (SD)	26.38 (7.37)	26.02 (7.16)	26.71 (7.49)	0.40
Completed training sessions (out of 6), mean (SD)	5.89 (0.36)	5.90 (0.33)	5.88 (0.38)	0.56
Percent success at 3-month follow-up	75.9%	77.3%	74.8%	0.63
Percent success at 1-year follow-up	61.6%	65.9%	58.4%	0.18

Note: Continuous variables were analyzed with two-group ANOVAs, with $F(1, 319)$. Categorical variables were analyzed with chi-square tests (df = 1). For all analyses, p-values were two-tailed, and alpha was set at 0.05. Standard deviations are presented in parentheses.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; SCL-90, Symptom Checklist-90.

[a]Education level was scored on a scale from 1 (primary school) to 5 (finished university).

Beck Depression Inventory (BDI)

We used the German version of the BDI (Hautzinger et al., 1994) to measure the severity of depressive symptoms. The BDI has high internal consistency (Cronbach's alpha = 0.80) and test–retest reliability ($r = 0.92$; Hautzinger et al., 1994).

Symptom Checklist 90–Revised (SCL-90-R)

The German version of the SCL-90-R (Franke & Stacker, 1995) contains 90 items that measure the physical and psychological impairment experienced during the past 7 days. Based on this, a global severity index is computed to indicate the overall level of

distress. The SCL-90-R has excellent internal consistency (Cronbach's alpha = 0.97; Franke & Stacker, 1995).

Picture materials

Sixty pictures of two drink types (30 alcoholic and 30 nonalcoholic beverages) from an East German picture set (den Uyl et al., 2017; Wiers et al., 2011) were used in SI-Training and alcohol-ApBM. To assess changes in the evaluation of pictures over the course of the trainings, we counterbalanced the pictures of each drink type across three categories: Ten alcoholic and 10 nonalcoholic pictures were not trained at all, 10 plus 10 pictures were trained in the alcohol-ApBM only, and 10 plus 10 pictures were trained in both the alcohol-ApBM and the SI-Training. This allowed us to assess effects of ApBM on the evaluation of alcoholic and nonalcoholic beverages (ApBM-trained vs. not trained), as well as additional effects of the SI-Training (SI- and ApBM-trained vs. ApBM-trained).

Experimental tasks

Alcohol–approach bias modification (Alcohol-ApBM)

The alcohol-ApBM used a similar setup as in previous studies (e.g., Rinck et al., 2018): In each of six training sessions, patients used a joystick to push 100 pictures of alcoholic beverages away (avoidance) and to pull 100 pictures of nonalcoholic beverages closer (approach). Most relevant for the current study, each training session started with 40 assessment trials during which both drink types were approached as well as avoided. From these trials, for each patient and session, we computed mean reaction times (RTs) for each of the eight combinations of drink type (alcohol and nonalcohol), training scheme of pictures (pictures trained in ApBM only and pictures trained in both ApBM and SI-Training), and movement (pull and push). ApBM compatibility scores were then calculated as the difference between training-incongruent movements (pulling alcohol and pushing nonalcohol) minus training-congruent movements (pushing alcohol and pulling nonalcohol), separately for both picture training types and the six training sessions. Positive scores indicate a training-compatible relative alcohol-avoidance tendency, and negative scores indicate a training-incompatible relative alcohol-approach tendency, with larger scores implying stronger tendencies.

Selective inhibition training (SI-Training)

The SI-Training required participants to press a computer key in response to pictures of nonalcoholic drinks (Go trials), and to withhold the reaction to pictures of alcoholic drinks (No-Go trials). In the current study, the SI-Training consisted of six sessions, each of which directedly followed the alcohol-ApBM. Within SI-Training, each training session consisted of four training blocks with 40 trials per block (160 trials per session). Trials were presented quasi-randomly with maximally four consecutive Go or No-Go trials. In each trial, a picture was presented for 1100 ms. At 100 ms after picture onset, a green frame (Go cue) or a red frame (No-Go cue) appeared and surrounded the picture. Participants were instructed to press the spacebar of the computer keyboard as quickly as possible when a Go cue was presented and to not respond when a No-Go cue was shown, irrespective of the content of the pictures. After a correct motor reaction in response to a Go cue, or no reaction in response to a No-Go cue, the picture disappeared. After incorrect responses, the German word for "error" appeared for 1 s. There was a fixed intertrial interval of 1 s. In both training conditions, there were 25% No-Go trials and 75% Go trials. In the active SI-Training, all alcoholic beverages were paired with the No-Go cues and all nonalcoholic beverages with the Go-cues. In the sham SI-Training, both alcoholic and nonalcoholic beverages were paired with both Go cues and No-Go cues. The very first session started with 12 practice trials using neutral pictures that were not used during training.

Picture evaluation

To assess changes in the evaluation of alcoholic and nonalcoholic beverages over the course of training, participants rated all 60 pictures before the first and after the sixth session. Following the procedure introduced by Chen et al. (2016), all drink pictures were rated on their attractiveness on a visual analog scale ranging from −100 to +100.

Experimental training groups

In the present RCT using a parallel design structure with an equal allocation ratio, 434 patients were randomly assigned to one of the two SI-Training conditions, using simple randomization stratified for gender. Specifically, participants were randomized to one of six conditions to counterbalance the picture types (as explained above) and to allocate them to active versus sham SI-Training. In Python, using PsychoPy 2.71 (Peirce et al., 2019), the random allocation sequence was generated by the first author by creating a randomized input list which was stratified for gender because the sample consisted mainly of males (65%). Using an output program programmed in Python, after entering the gender and assigned ID of a patient, the experimenter was given the training condition of the patient, adhering to aforementioned requirements. Of all 434 patients, 214 were assigned to the active SI-Training, and 220 to the sham SI-Training. Within each training condition, the pictures were counterbalanced across the three picture conditions.

Statistical analyses

For our primary outcome (success rates of being abstinent at follow-ups after 3 months and 1 year), we used chi-square tests to

compare the percentages of successes versus failures in the two training groups to each other. Specifically, adhering to the guidelines of the German Addiction Society, we first computed intention-to-treat (ITT) analyses (i.e., analyses according to DGSS4 standard). These were followed by analyses including only the patients who were reached at the respective follow-up (i.e., analyses according to DGSS1 standards). Finally, we computed per-protocol analyses, including only those patients who had both completed the training and were reached at follow-up.

For our secondary outcomes (changes in the evaluation of alcohol due to SI-Training, training effects of the SI-Training, and changes in alcohol approach bias), we employed mixed-factor ANOVAs. To assess the evaluation of both alcoholic and nonalcoholic drink pictures before training as well as changes in their evaluations, we first computed each participant's mean rating for each drink type (alcohol and nonalcohol) and each training scheme of pictures (untrained, trained in ApBM only and trained in both ApBM and SI-Training) at each assessment point (prerating and postrating). To test for pre-experimental differences in ratings, we conducted a 2 (training group: active and sham)×2 (drink type: alcohol and nonalcohol)×3 (training scheme: untrained, trained-in-ApBM, and trained-in-ApBM and -SI) mixed-factors ANOVA of the picture evaluations before training.

To examine differences in changes in evaluations over time, we conducted two mixed-factors ANOVAs, separately for alcohol and nonalcohol pictures. They included the between-subjects factor training group (active vs. sham SI-Training) and the within-subjects factors training scheme (untrained, trained-in-APBM, and trained-in-ApBM and -SI) and time (prerating and postrating).

For SI-Training, at baseline, we conducted an ANOVA with the between-subjects factor training group (active vs. sham SI-Training) on the Go trials at session 1. To assess changes in the responses to the Go trials of the participants from the first to the last session, we conducted a 2 (training group: active and sham)×2 (time: session 1 and session 6) mixed-factors ANOVA.

For ApBM, to test for pre-experimental differences in approach avoidance tendencies, we conducted *t*-tests for independent samples using the stats package in R (R Core Team, 2020). To exploratively investigate changes in approach bias toward alcohol after alcohol-ApBM training, we conducted a mixed-factors ANOVA with the between-subjects factor training group (active SI-Training and sham SI-Training) and the within-subjects factors time (session 1 to session 6) and training schemes (ApBM, ApBM- and SI-Training) on the ApBM compatibility effects. All mixed-factors ANOVAs were computed using the aov_ez function of the *afex* package in R (Singmann et al., 2016). For all analyses, required assumptions were checked and deviations are reported in the text below. The Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. All analyses were performed in R (R Core Team, 2020). All analyses used two-sided tests with $p = 0.05$.

RESULTS

Overall, 74.0% (321 of 434) of the patients finished the prescribed six sessions of combined training.

Treatment outcome: effects of the SI-Training on 3-month and 1-year follow-up outcomes

At *3-month follow-up*, 300 patients could be reached (69.1%), and 293 of them (67.5%) were willing to provide information about clinical outcome. Success rates per group based on all 434 patients are given in Table 1, showing an overall success rate of 49.8%. Against our hypothesis, there was no significant difference between the success rates of the two training groups after 3 months, when adhering to DGSS4 criteria, $\chi^2(1) = 0.18$, $p = 0.66$, $\phi = 0.02$. Likewise, the DGSS1 analysis (including only the 293 patients who were reached at 3-month follow-up and were willing to provide information. The groups did not differ in aforementioned demographic characteristics. For an overview, see the Table S1), did not reveal evidence for a difference in success rates between the two training groups either, $\chi^2(1) = 0.00$, $p = 0.98$, $\phi = 0.00$. Similarly, the per-protocol analysis (including only the 216 patients who had completed the full training and were reached at 3-month follow-up) did not show a difference between the groups either, $\chi^2(1) = 0.22$, $p = 0.63$, $\phi = -0.03$.

Comparable results were observed for the *1-year follow-up*: A total of 317 patients were reached (73.0% of 434), and clinical outcomes were obtained from 294 of them (67.7% of 434). The overall success rate was 42.6%, and success rates per group are shown in Table 1. The ITT analysis of these success rates according to DGSS4 criteria ($n = 434$) revealed no difference between the two training groups, $\chi^2(1) = 0.24$, $p = 0.62$, $\phi = 0.02$. The analysis of the success rates according to DGSS1 ($n = 294$) revealed no difference between the two training groups either, $\chi^2(1) = 1.09$, $p = 0.30$, $\phi = -0.06$, neither did the per-protocol analysis ($n = 216$), $\chi^2(1) = 1.79$, $p = 0.18$, $\phi = -0.09$.

Secondary outcomes

Devaluation effects

Baseline evaluations

Before training, the picture evaluations did not differ significantly between the two training groups, $F(1, 319) = 0.22$, $p = 0.643$, $\eta_p^2 < 0.001$, neither did the evaluations of the three-picture training scheme conditions, $F(1.94, 620.09) = 0.27$, $p = 0.757$, $\eta_p^2 = 0.000$. Not as expected, however, there was a highly significant main effect of drink type, $F(1, 319) = 246.09$, $p < 0.001$, $\eta_p^2 = 0.435$, showing a negative mean evaluation of alcohol, compared to a fairly neutral

evaluation of nonalcoholic drinks. Table 3 shows an overview of the ratings of the drink types, both overall and per training groups, and training scheme conditions at baseline and post-test.

Changes in the evaluation of drink types

Changes in the evaluation of alcohol

The expected three-way interaction of experimental group, time, and training scheme was not significant, $F(1.99, 636.38) = 0.66$, $p = 0.514$, $\eta_p^2 = 0.002$. In contrast to our predictions, there was no significant difference between the experimental groups in their evaluation of alcohol pictures, $F(1, 319) = 1.75$, $p = 0.187$, $\eta_p^2 = 0.005$. Moreover, the evaluations of the alcohol pictures did not differ depending on how they had been trained, $F(1.95, 620.95) = 0.04$, $p = 0.954$, $\eta_p^2 = 0.000$, and the evaluations did not change significantly over time, $F(1, 319) = 2.03$, $p = 0.155$, $\eta_p^2 = 0.006$. Comparable to the baseline evaluations, alcohol remained negatively evaluated posttraining ($M = -49$, SD = −56). See Table 3 for means and standard deviations.

Changes in the evaluation of nonalcoholic drinks

There was a significant main effect of time, $F(1, 319) = 10.86$, $p < 0.001$, $\eta_p^2 = 0.033$, indicating that the evaluations of nonalcoholic drinks became more positive over time (pre: $M = 1.90$, SD = 65, post: $M = 7.80$, SD = 63). However, this time effect did not interact with any other effect; it was the same for nonalcoholic pictures being trained in the ApBM only, in both tasks, or being untrained, $F(1.99, 633.75) = 0.51$, $p = 0.599$, $\eta_p^2 = 0.002$, and it was the same for both experimental groups, $F(1, 319) = 0.27$, $p = 0.605$, $\eta_p^2 = 0.000$. Table 3 shows an overview of the changes in the evaluations of the drink types.

Manipulation checks: effects of SI-Training and ApBM training

Performance in the SI-Training

Overall, accuracy rates were high, yielding an average of 98.6%. With regard to response speed on Go trials, there was no difference between the active training ($M = 442$ ms, SD = 105.00) and the sham training group ($M = 443$ ms, SD = 102.10) at baseline in Session 1, $F(1, 319) = 3.42$, $p = 0.065$, $\eta_p^2 = 0.011$. Patients in the active training group (M session 6 = 418 ms, SD = 87.52) became faster in their responses to the Go stimuli, $F(3.23, 423.26) = 22.13$, $p < 0.001$, $\eta_p^2 = 0.145$, as did patients in the sham training group (M session 6 = 434 ms, SD = 96.10), $F(3.59, 995.49) = 31.89$, $p < 0.001$, $\eta_p^2 = 0.103$, indicating that participants became more proficient in executing the task. The acceleration of responses to the Go cues over time was stronger in the active training group than in the sham group, $F(3.6, 993.57) = 3.16$, $p = 0.017$, $\eta_p^2 = 0.011$.

ApBM training

Baseline approach bias

Before ApBM, there was no difference between participants in the active training group ($M = -58$, SD = 343.00) and those in the sham training group ($M = -50$, SD = 340.77) regarding their approach bias toward alcohol, $t(319) = 0.209$, $p = 0.835$. Both groups showed a significant approach bias; as indicated by their negative ApBM scores which deviated significantly from zero, both for the active SI-Training group, $t(149) = 2.69$, $p = 0.008$, and for the sham SI-Training group, $t(170) = 3.36$, $p < 0.001$.

TABLE 3 Mean evaluations of drink stimuli at baseline and after training: means (SDs).

	Alcoholic drinks, mean (SD)		Nonalcoholic drinks, mean (SD)	
Drink evaluations	**Baseline**	**Postassessment**	**Baseline**	**Postassessment**
Evaluation overall	−52.00 (55.00)	−48.86 (55.70)	1.90 (65.00)	7.78 (63.20)
Evaluation per training condition				
Active SI-Training ($n = 150$)	−54.40 (54.00)	−52.41 (54.50)	2.80 (65.00)	9.64 (64.40)
Sham SI-Training ($n = 171$)	−49.80 (56.00)	−45.74 (56.40)	1.10 (65.00)	6.15 (62.00)
Evaluation per training scheme condition				
Untrained (overall)	−51.92 (55.40)	−48.90 (55.30)	2.03 (65.10)	7.23 (63.30)
Untrained (active SI-Training)	−53.40 (54.80)	−51.87 (54.80)	2.37 (64.90)	8.55 (65.0)
Untrained (Sham SI-Training)	−50.61 (55.90)	−46.30 (55.70)	1.72 (65.30)	6.05 (61.90)
Trained-in-ApBM (overall)	−51.73 (55.20)	−49.29 (55.10)	2.19 (65.30)	8.19 (62.70)
Trained-in-ApBM (active SI-Training)	−54.16 (54.20)	−53.02 (53.90)	2.78 (64.80)	10.19 (63.90)
Trained-in-ApBM (Sham SI)	−49.59 (55.90)	−46.01 (55.90)	1.66 (65.90)	6.42 (61.50)
Trained-in-ApBM and -SI-Training (overall)	−52.19 (54.80)	−48.90 (55.30)	1.50 (65.1)	7.93 (63.30)
Trained-in-ApBM and -SI-Training (active SI-Training)	−55.71 (53.0)	−52.34 (55.00)	3.15 (65.30)	10.15 (64.30)
Trained-in-ApBM and -SI-Training (Sham SI-Training)	−49.09 (56.10)	−44.91 (57.70)	0.05 (65.00)	5.96 (62.60)

Approach bias change

The bias scores showed a significant main effect of time, $F(4.56, 1455.82) = 19.49$, $p < 0.001$, $\eta_p^2 = 0.058$, indicating that over time, the patients' alcohol approach bias turned into an alcohol avoidance bias (M-pretest = −54.1, SD = 341.72, M-posttest = 32.3, SD = 240.20). This change was similar for both experimental groups, however, $F(4.56, 1455.82) = 1.50$, $p = 0.192$, $\eta_p^2 = 0.005$. In addition, there was a significant main effect of training type, $F(1, 319) = 14.48$, $p < 0.001$, $\eta_p^2 = 0.043$. Unexpectedly, pictures trained solely in the ApBM ($M = 48.25$, SD = 7.91) overall showed a stronger alcohol avoidance bias than pictures trained in both ApBM and SI-Training ($M = 3.32$, SD = 7.62).

DISCUSSION

In the current study, we investigated whether the clinical effects of regular treatment for alcohol use disorder (AUD) including ApBM could be enhanced by simultaneously targeting the evaluation of alcohol via selective inhibition training (SI-Training). In contrast to expectations, SI-Training did not affect the patients' evaluations of alcoholic or nonalcoholic drinks, regardless of whether patients were trained with active or sham SI-Training on top of active ApBM. Before training, nonalcoholic beverages were generally rated positively, and alcoholic beverages were generally rated negatively. While the evaluation of nonalcoholic drink pictures became even more positive after the training, the rating of alcoholic pictures remained equally negative after training. Mirroring the null effects on the evaluation of alcohol pictures, SI-Training did not reduce relapse rates at follow-up after 3 months or 1 year. Finally, ApBM changed the alcohol approach tendency into an avoidance tendency, but it made no difference whether or not the evaluation of alcohol was additionally targeted by SI-Training. Therefore, the present results do not support the hypothesis that the relapse-preventing effects of treatment can be amplified by SI-Training, or does it seem to affect the evaluation of alcohol stimuli or the approach bias toward them.

The absence of a devaluation effect of alcohol after SI-Training in the present context contrasts with earlier studies which found SI-Training to devalue alcohol in social drinkers (Bowley et al., 2013; Houben et al., 2011, 2012; Jones & Field, 2013). In the present study, although nonalcoholic drinks were evaluated more positively after SI-Training, alcoholic drinks remained as negative as they were at baseline. This suggests a floor effect: SI-Training may have devalued the alcohol pictures, but this could not be detected because the ratings for alcohol stimuli were already at the low end of the scale. Interestingly, the absence of devaluation of alcohol after ApBM is in line with similar results in social drinkers reported by Wiers et al. (2010). This may be related to the incentive salience of alcohol cues (the motivation to approach alcohol or "wanting"), which is strongly intertwined with the subjective liking of alcohol ("liking," or evaluation). In combination, this may lead to a stronger approach motivation toward alcohol. Importantly, however, a strong alcohol approach tendency can occur both with or without subjective liking of alcohol (Berridge & Robinson, 2016; Palfai & Ostafin, 2003; Wiers et al., 2009). Thus, it might be that alcohol consumption by patients with AUD is more driven by "wanting" than "liking" alcohol, whereas consumption by social drinkers might be driven by both, with the (positive) evaluation of alcohol playing a more prominent role.

Simultaneously, Dickson et al. (2013) found that, while not differing in positive associations with alcohol, patients with AUD had relatively weaker negative associations with alcohol than social drinkers, warranting more research into this issue. For ApBM, in line with earlier studies (Eberl et al., 2014; Rinck et al., 2018; Wiers et al., 2011), ApBM changed the approach bias for alcohol stimuli, but there was little evidence of an effect on valence.

Furthermore, adding SI-Training to regular treatment for AUD (including ApBM) yielded no additional reduction in relapse rates at either 3 or 12 months after discharge from treatment. The absence of devaluation of alcohol together with a null effect on behavior contrasts with the findings of previous studies (Bowley et al., 2013; Houben et al., 2011, 2012; Jones & Field, 2013). In these studies, SI-Training changed the evaluation of alcohol and also reduced the short-term consumption of alcohol by social drinkers. Furthermore, several studies showed that changed evaluations of various appetitive stimuli, including alcohol, led to reduced consumption (Houben et al., 2012; Veling et al., 2017). Based on these promising results and a study by Di Lemma and Field (2017) reporting that both alcohol-ApBM and SI-Training successfully reduced alcohol consumption in heavy-drinking individuals, we transferred this approach to the domain of relapse prevention in abstinent alcohol-dependent patients. However, despite applying a protocol that has previously been sensitive to picking up effects of the training on evaluations (Chen et al., 2016; Di Lemma & Field, 2017; Lawrence et al., 2015; Veling et al., 2008; Wessel et al., 2014), we did not find an effect on evaluations or treatment outcome. Note, however, that for ethical reasons, we could not include a measure of alcohol consumption, unlike earlier studies.

When it comes to inhibitory control itself, the current study did not find any indications of general improvements in inhibitory control, which is compatible with the hypothesis that *selective* inhibition training primarily works through devaluation of the inhibited category and not through an increase in general inhibitory control (Houben et al., 2012; Veling et al., 2008; Wiers, 2018). In the present SI-Training, while the responses became faster over time—with a larger change in the active than the sham SI-Training—there were almost no commission errors made by the participants, or were there differences in the responses to alcoholic and nonalcoholic beverages in the sham SI-Training. Therefore, next to the lack of evidence for the devaluation hypothesis (Veling et al., 2008), the present study does not support the hypothesis of general improvements in inhibitory control either. This is in line with earlier mixed findings regarding the effects of inhibitory training on drinking behavior in alcohol dependence (Batschelet et al., 2020).

To potentially increase the difficulty of the SI-Training, and thereby its effectiveness, future studies might reduce the frequency of No-Go cues paired with alcoholic beverages compared to the current study. In our study, the active SI-Training version contained 25% No-Go trials because we wanted to present a sufficient number of alcohol–No-Go combinations. Still, this might have reduced the response conflict between the approach tendency toward the alcohol picture and the required inhibition of the response to it, diminishing the devaluation of alcohol. Previous studies contained fewer No-Go trials, which may have strengthened the devaluating effect of inhibition on the stimuli associated with No-Go trials. Moreover, a more difficult No-Go cue might be used to increase the effect further (see, for instance, Stein et al., 2021, 2023; Tschumperlin et al., 2019).

Additionally, future studies should investigate whether the use of both explicit and implicit measures of evaluation allows for a more fine-grained assessment of the evaluation changes caused by SI-Training.

This study has several limitations. First, as the study was conducted as an RCT within a clinical context, it is unfortunate that a large amount of postrating data were lost due to technical issues. Also, information on changes in evaluation and abstinence rates after treatment might be affected by dropout both during training and after discharge from clinical treatment, which may have prevented a clearer picture of the effects of ApBM–SI-Training on abstinence rates. Further, the current study limited itself to assessing whether the ApBM–SI-Training combination would reduce relapse rates, without creating a control condition without ApBM. The latter was impossible because, after several RCTs with positive results, ApBM is now part of regular treatment. Moreover, following research in the domain of impulsive eating behavior (Kakoschke et al., 2017b), we limited ourselves to an explicit measure of evaluation, excluding potentially informative implicit measures. Furthermore, we did not include any other measure of liking, craving, or wanting of the alcohol stimuli, although this might have shed more light on the effects of SI-Training. Furthermore, as the study was embedded into clinical practice, we had to employ the outcome definitions of abstinence defined by the German Addiction Society. For practical reasons, we were unable to include a more detailed assessment of posttreatment drinking behavior (e.g., duration of lapses, amount of consumption in case of relapse, and number of abstinent days). Finally, we had to rely solely on self-report information for assessing abstinence at follow-ups, and we could not include any biological measures of abstinence after treatment.

Despite these limitations, the current study also has several strengths. The study was conducted as a large-scale RCT in a clinical sample, which is often impossible in CBM research. It yielded sufficient statistical power to detect and replicate the effects of CBM interventions, which are usually small effects, on clinically relevant outcomes (Rinck, 2017). Further, as our study employed multiple sessions of SI-Training and a very long follow-up interval (1 year), it allows for inferences about the long-term effects of SI-Training. These cannot be assessed in laboratory experiments or proof-of-principle studies which usually involve a single training session and short follow-up intervals.

This study provides a first indication of the clinical effectiveness of adding SI-Training to the treatment of alcohol use disorder to reduce relapse rates after treatment. This fills an important gap regarding the clinical effects of inhibition trainings, particularly the effects on drinking behavior in alcohol-dependent individuals motivated to remain abstinent. While we found no evidence for a beneficial effect, we suggest not to give up this area of research prematurely. Instead, large-scale studies with sufficient statistical power like the one reported here should be conducted to determine if the limitations mentioned above caused the observed null effects. Moreover, applications of SI-Training to situations other than relapse prevention in abstinent AUD patients should be explored, for instance, reduction of consumption in heavy drinkers.

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CONFLICT OF INTEREST STATEMENT

Johannes Lindenmeyer declares to be the Chief Executive Officer (CEO) of the clinic at the time the study was conducted. All other authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

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