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RESEARCH REPORT

ADDICTION SSA

Alcohol-specific inhibition training in patients with alcohol use disorder: a multi-centre, double-blind randomized clinical trial examining drinking outcome and working mechanisms

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Abstract

Aims: For the first time, to our knowledge, in a clinical sample with alcohol use disorder (AUD), this study compared the effects of two versions of alcohol-specific inhibition training (Alc-IT) on drinking outcomes and on experimental parameters assessing two possible working mechanisms: stimulus devaluation and inhibitory enhancement.

Design: Multi-centre, double-blind, three-arm clinical RCT with 3-, 6- and 12-month follow-up comparing standard Alc-IT, improved Alc-IT and an active control condition.

Setting: Three specialized AUD treatment centres in Switzerland.

Participants: A total of 242 detoxified, recently abstinent patients with severe AUD (18–60 years; 29.8% female).

Intervention and Comparator: Both interventions [standard Alc-IT (n = 84) and improved Alc-IT (n = 79)] and the comparator [unspecific inhibition training (n = 79)] consisted of six sessions of a modified inhibitory task (Go/NoGo task) with alcohol-related and neutral stimuli. Both versions of Alc-IT required response inhibition in alcohol-related trials but differed in Go/NoGo ratios (standard: 50/50; improved: 75/25), with improved Alc-IT posing higher inhibitory demands. The control condition, an unspecific inhibition training, featured alcohol-related pictures in Go as well as NoGo trials.

Measurements: The primary outcome, percentage of days abstinent, was assessed at 3-month follow-up with a time-line follow-back interview.

Findings: The group receiving improved Alc-IT showed a significantly higher percentage of days abstinent at 3-month follow-up compared with the control group [$\gamma_{control}$ = 74.30; $\gamma_{improved}$ = 85.78; β = 11.48, 95% confidence interval (CI) = 2.57, 20.40, P = 0.012, adjusted r^2 = 0.062], while for standard Alc-IT no effect significantly different from zero was detected ($\gamma_{standard}$ = 70.95; β = −3.35, 95% CI = −12.20, 5.50, P = 0.457, adjusted r^2 = −0.04).

† These authors contributed equally to this work.

Conclusions: Alcohol-specific inhibition training with high inhibitory demands increased days abstinent at 3-month follow-up in patients with severe alcohol use disorder. Such an improved, inhibitory-demanding, alcohol-specific inhibition training outperformed the standard version of alcohol-specific inhibition training, suggesting an inhibitory working mechanism.

KEYWORDS

Addiction, alcohol use disorder, clinical trial, cognitive bias modification, drinking outcomes, implicit associations, inhibition, psychotherapy, training, working mechanism

INTRODUCTION

Relapse rates after residential treatment programmes for alcohol use disorder (AUD) are high. Various computerized training interventions, including approach bias modification, attentional bias modification and alcohol-specific inhibition training, have been proposed as a cost-effective add-on to relapse prevention treatment [1–3]. Because AUD is characterized by both deficient inhibitory control and enhanced cue-reactivity or drinking urges induced by alcohol-related stimuli, these computerized training interventions typically aim either to reduce biases related to enhanced cue-reactivity or to improve inhibitory capacities. Approach-bias modification has been shown to improve treatment outcomes throughout several clinical randomized controlled trials (RCTs [4–7]), while attentional bias modification yielded less consistent results, with some clinical RCTs reporting positive results [6,8], others not [9–11]. The third type of training, alcohol-specific inhibition training (Alc-IT), has currently only been investigated in healthy volunteers. Some of these studies suggested that Alc-IT might reduce drinking as assessed up to 2 weeks after training [12–14]; others observed no positive effects [15,16] or mixed results [17,18]. These inconsistencies might be due to variations in setting (on-line versus on-site), level of alcohol-related problems and motivation of participants [3,19]. Studies on Alc-IT in clinical samples or with longer follow-up intervals are lacking.

In Alc-IT, participants are required to react to pictures with a button press (Go trials) unless a NoGo cue is presented (NoGo trials [13]). Alcohol-related pictures are consistently paired with the NoGo cue, thus prompting participants to inhibit their response to alcohol-related stimuli. Notably, with one exception [15], all prior studies tested Alc-IT with a Go/NoGo ratio of 50/50, thus an equiprobable distribution of Go and NoGo trials, which possibly makes inhibition less strenuous and might reduce training effects. In contrast, most studies identifying inhibitory deficits in AUD used higher Go/NoGo ratios (e.g. 75/25), thereby creating a high response pre-potency and making inhibition more difficult [20]. A higher Go/NoGo ratio may therefore increase the beneficial effects of Alc-IT.

Two potential working mechanisms have been proposed. Alc-IT may work either by enhancing the inhibitory control [21], a mechanism potentially traceable through performance on inhibitory control tasks or, alternatively, the stimulus devaluation hypothesis [22] proposes that consistently pairing a stimulus with a stopping response (as required for alcohol-related stimuli in the Alc-IT) decreases the stimulus' valence and motivational properties, thus affecting implicit, automatic associations towards alcohol [12]. To date, information on these experimental parameters is limited and inconclusive [3]. The effects of Alc-IT on implicit associations, as postulated by the stimulus devaluation hypothesis, have been reported in two [12,13] but not in four other pre-clinical studies [14,15,23,24]. The effects of Alc-IT on inhibitory control have been confirmed in one study [25], compared to three studies reporting no effect [12,14,23]. Notably, all these studies used the standard variant of Alc-IT with Go/NoGo ratios of 50/50, thereby possibly limiting inhibitory effects.

For the first time in a clinical sample, the aim of this double-blind RCT was (i) to compare the change in drinking outcome induced by the standard Alc-IT and by an improved, inhibitory more demanding, variant of Alc-IT against an active control condition to test whether Alc-IT reduces drinking. Secondary aims were (ii) to compare the change in alcohol-specific inhibitory control induced by the two versions of Alc-IT against the control condition to test whether Alc-IT operates via changes in inhibitory control; (iii) to compare the change in alcohol-specific inhibitory control induced by improved Alc-IT against standard Alc-IT to test the hypothesis that improved Alc-IT yields stronger inhibitory effects than standard Alc-IT; and (iv) to compare the change in alcohol-related implicit associations induced by the two versions of Alc-IT against the control condition to test whether Alc-IT activates a devaluation-based working mechanism.

METHODS

Design

In this multi-centre, double-blind, clinical RCT, two versions of a computerized Alc-IT were tested against an active control condition in recently abstinent, detoxified patients with AUD attending a specialized residential treatment programme for AUD [26]. In standard Alc-IT, Go and NoGo trials occurred equally often (50/50); in improved Alc-IT, a Go/NoGo ratio of 75/25 was used with the aim of making inhibition more strenuous, thus enhancing training effects. Both versions were tested against a non-specific inhibition training (i.e. an active control condition). As an additional experimental manipulation, participants received their allocated training version either in the morning or in the afternoon, to test whether the daytime of training moderated training effects due to variations in endogenous cortisol (see also the on-line Supporting information, 1.1.2). The allocated training version was administered as an add-on to the residential treatment programme. Pre- and post-training assessments during residential treatment were used to monitor secondary outcomes related to Alc-ITs working mechanism. After discharge from residential treatment, assessment of the primary outcome took place at 3-month follow-up. The 3-month follow-up was chosen as primary outcome because it provides clinically relevant data on a very vulnerable phase with high relapse rates [27–29]. Also, the time-point minimizes the risk of missing experimental effects because they either are transient or become diluted by uncontrolled influences. In order to be able to conduct exploratory assessments of the temporal stability of potential effects, additional follow-up assessments (to be reported elsewhere) were scheduled at 6- and 12-month follow-up.

Procedure and randomization

Eligible patients were contacted upon admission to residential treatment. After assessing the inclusion/exclusion criteria and obtaining written informed consent, a baseline measurement during the second treatment week comprised questionnaires, diagnostics and a time-line follow-back (TLFB [32]) interview. At the end of the third treatment week, a pre-training assessment comprised questionnaires and experimental tasks assessing inhibitory control (Go/NoGo task and stop signal task) and implicit associations (implicit associations test). An independent investigator randomly assigned the participants to one of the three training interventions and one of the two daytimes of training (morning/afternoon). Block randomization with variable block sizes was stratified according to gender and age (age groups: 18–25, 26–35, 36–45, 46–55 and 56–60) and was implemented following a randomization list, which was generated with MATLAB (version 2017a; Mathworks, Natick, MA, USA) and stored in a locked place by the independent investigator; thus participants, investigators, care providers and members of the study team were blind to the allocation schedule. During treatment weeks 4 and 5, all participants completed six short (approximately 10–15 minutes) training sessions of their allocated condition (standard Alc-IT, improved Alc-IT or control training). At the end of each training session, the participants' average reaction-times and error rates were communicated to maintain motivation. In a post-training assessment 1–4 days after the last training session, all measures of the pre-training assessment (including Go/NoGo-task and implicit association test) were repeated. Patients then completed their inpatient stay, with treatment programmes planned to last approximately 8–12 weeks. Upon discharge, a questionnaire battery was administered. Three months after treatment discharge, all participants were contacted by telephone and mail to assess the primary and secondary outcome variables for the 3-month follow-up in a short telephone interview, a TLFB interview and a questionnaire battery (see [26] for detailed study protocol). A less extensive follow-up assessment was repeated 6 and 12 months after discharge (to be reported elsewhere). The study was approved by the local ethics committees of the study sites (No.: 2016_000988) and was registered with ClinicalTrials.gov (NCT02968537).

Participants

Of the 753 patients assessed for eligibility, 548 met the inclusion criteria. Of these, 197 refused to participate and 109 patients

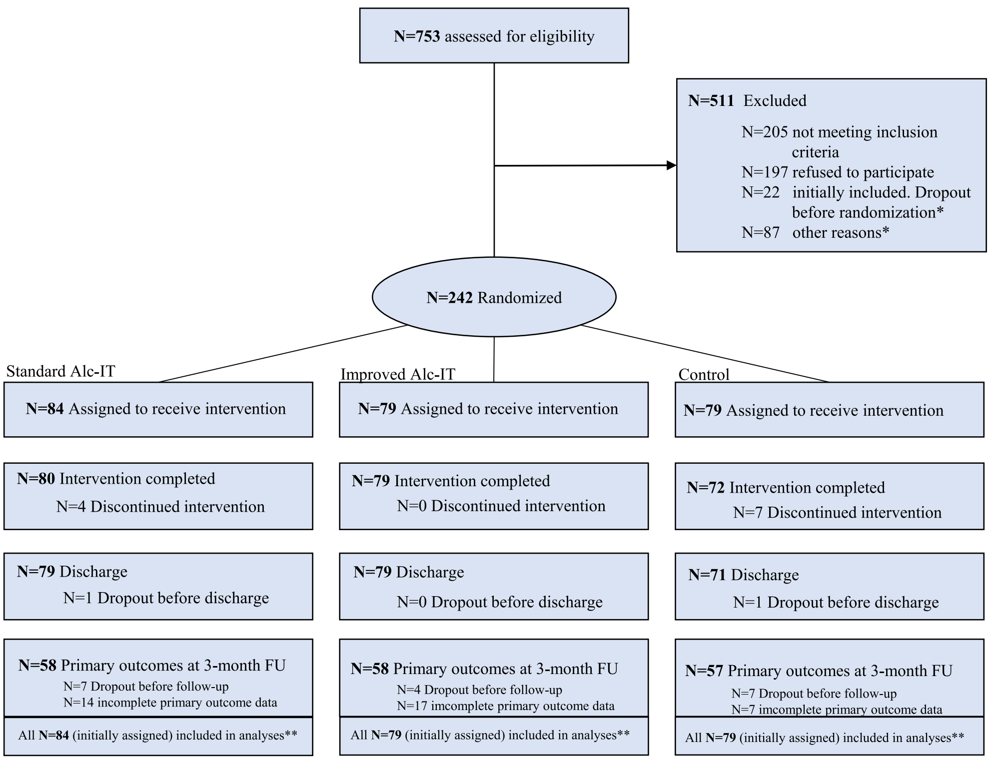

FIGURE 1 Consort flow diagram. *Reasons being, for example, unexpected discharge from inpatient treatment, organizational difficulties to align the study procedure with the patient's agenda, acute infectious illness or somatic complications; **for the conservative intention-to-treat analyses, all patients initially assigned were retained in the analyses of primary outcomes. Standard Alc-IT = alcohol-specific inhibition training with a Go/NoGo ratio of 50/50; improved Alc-IT = alcohol-specific inhibition training with a Go/NoGo ratio of 75/25; control = unspecific control training; FU = follow-up

could not participate, mainly for organizational reasons (Figure 1). Finally, 242 detoxified patients attending an abstinence-orientated residential treatment programme for AUD at one of three specialized addiction treatment centres in Switzerland were included in the study between 2015 and 2019 after obtaining their written informed consent. The inclusion criteria were AUD diagnosis, aged 18–60 years and abstinence from alcohol for at least 4 weeks prior to the first training session. The exclusion criteria were main psychiatric diagnoses other than AUD (comorbidities were allowed as long as AUD was the primary diagnosis), other severe substance use disorder [except nicotine; Drug Use Disorder Identification Test (DUDIT) ≥ 25 per substance [30])], neurocognitive problems (e.g. Korsakoff syndrome), current medical conditions preventing participation (e.g. acute infectious diseases) and insufficient language skills. To conduct conservative intention-to-treat analyses, all 242 subjects were retained in the analyses on drinking outcomes. A priori power analyses with G*power (version 3.1.5, Duesseldorf, Germany) indicated a necessary sample size of 244 to detect a small to medium effect of the training interventions given $\alpha = 0.05$ and $1\beta = 0.8$ [26].

Training intervention

All three training interventions included 320 trials: 80 trials comprising pictures of alcoholic beverages (tailored to the drink of choice), 80 water trials and 160 trials with pictures of neutral objects. In all three training versions, participants were instructed to press a button when a Go cue appeared next to the picture and to withhold from responding when a NoGo cue appeared (see also Table 1 and Supporting information, 1.3).

In both versions of the alcohol-specific inhibition training (Alc-IT), pictures of alcoholic beverages were consistently paired with a NoGo cue, while Go cues were distributed among other picture types (water, neutral). In contrast, in the control training, an unspecific inhibition training, all three picture types were distributed equally throughout Go and NoGo trials. Both versions of Alc-IT were alcohol-specific, comprised equal numbers of alcohol-NoGo pairings (i.e. the stimulus devaluation component) and were of equal length. However, they differed in the Go/NoGo ratio and thus in the demands placed on the inhibitory system: standard Alc-IT operated with a Go/NoGo ratio of 50/50, as introduced to research on AUD by Houben *et al.* [13] and implemented in most pre-clinical studies. Improved Alc-IT operated with a Go/NoGo ratio of 75/25, thus creating a pre-potent response tendency and thereby higher inhibitory difficulty. The development of improved Alc-IT was inspired by research indicating that a higher Go/NoGo ratio increases the inhibitory demands [31] and might thus optimize training effects. Furthermore, studies describing inhibitory deficits in AUD often used higher Go/NoGo ratios (and reported higher effect sizes when doing so [20]), thus training with a high Go/NoGo ratio might target specific deficits in AUD more precisely.

Outcome measures

Primary outcome: percentage of days abstinent at 3-month follow-up

The quantity of daily alcohol consumption was assessed at baseline (assessing drinking 90 days prior to detoxification entry) and 3-month follow-up (assessing drinking 90 days following treatment discharge) using the TLFB [32].

TABLE 1 Overview of training characteristics and trials per condition for the three training versions

(A) Characteristics of the three training versions

	Standard Alc-IT Alcohol-specific inhibition training (Go/NoGo-ratio: 50/50)	Improved Alc-IT Alcohol-specific inhibition training (Go/NoGo-ratio: 75/25)	Control training Unspecific inhibition training (Go/NoGo-ratio: 50/50)
Alcohol-specific	Yes	Yes	No
Stimulus devaluation component (i.e. exclusive pairing of alcohol and NoGo-cues)	Yes	Yes	No
Inhibitory demands	Low	High	Low

(B) Number of trials per condition in the three training versions

	Standard Alc-IT		Improved Alc-IT		Control training	
	Go	NoGo	Go	NoGo	Go	NoGo
Alcohol	–	80	–	80	40	40
Water	80	–	80	–	40	40
Neutral	80	80	160	–	80	80
Total number of trials	320		320		320	

Alc-IT = alcohol-specific inhibition training.

Using this information, the percentage of days abstinent was calculated as the percentage of days without alcohol use, with an adjusted formula controlling for days spent in a protected environment (e.g. inpatient detoxification, see Supporting information, 1.5.2).

Focusing on the percentage of days abstinent at 3-month follow-up as a single primary outcome poses a deviation from the trial registration, in which multiple primary outcomes were listed (percentage of days abstinent, however, always being the first one; see Supporting information, 1.1.1). This deviation is required in order to adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [33].

Secondary outcomes

Secondary drinking outcomes were the percentage of heavy drinking days at 3-month follow-up, which was assessed in the same manner as the primary outcome, and time to first drink, which was assessed using the TLFB data from 3-month follow-up. To investigate working mechanisms, the two secondary outcomes, inhibitory control (as indicated by alcohol-specific errors of commission in the Go-NoGo task) and implicit associations (as indicated by the d-score from the implicit association test), were measured during a pre- and post-training assessment (for other secondary outcomes, see Supporting information, 1.1.1).

Questionnaires and interviews

At baseline, the AUD diagnosis was verified with the Diagnostic Expert System for Psychiatric Disorders (DIA-X, the AUD part adapted to DSM-5 [34]). Self-rated AUD symptoms (Alcohol Use Disorder Scale, AUD-S, adapted to DSM-5 [35]) were assessed in addition to other relevant clinical characteristics and demographics (see also Supporting information, 1.5.1 and [26]).

Experimental tasks and stimuli

Alcohol-related stimuli were tailored to the patients' drink of choice (either beer, wine or spirits) in all training versions and experimental tasks [26,36]. See Supporting information, 1.4 for details on stimuli and experimental tasks.

Conceptually close (but not identical) to the training, the Go/NoGo task (GNG) measured the action restraint component of response inhibition in an alcohol-specific as well as a neutral context [37,38], with alcohol-related errors of commission (i.e. failures to inhibit button presses on NoGo trials) serving as outcome variable to assess a potential inhibitory working mechanism.

To investigate the second potential working mechanism, the stimulus-devaluation hypothesis, an implicit association test (IAT) measured the strength of implicit associations between alcohol and positive or negative attributes [39,40], with positive d-scores indicating positive implicit associations towards alcohol.

Statistical analyses

Primary outcome

To analyse training effects on the primary outcome percentage of days abstinent at 3-month follow-up, a regression analysis was conducted using training intervention as a predictor and percentage of days abstinent at baseline as a covariate. To test for site heterogeneity, the interaction of site and training intervention was included as a predictor. The effect of the daytime of training and its interaction with the training interventions as well as potential confounding variables (i.e. age, gender, days in residential treatment and pharmacotherapy) were evaluated for inclusion in additional regression models. Little's MCAR test was significant ($\chi^2_{(69,\ n=242)} = 41.00$, $P = 0.0012$), but comparisons of the subgroup with and without missing values yielded no indicators of differences in their distributions (see Supporting information, 1.7.1), therefore missing at random (MAR) was assumed and multiple imputations by chained equations were used to address missing TLFB data. Sensitivity analyses using alternative missingness mechanisms assumptions [not missing at random (MNAR), missing completely at random (MCAR)] were also conducted (see Supporting information, 2.2). In the main analyses, both Alc-IT versions were tested against the control condition in a combined model.[1] The critical alpha level was adjusted according to a Bonferroni correction to control for the family-wise error rate, given the two comparisons of the three-arm trial (0.05/2 = 0.025).

Secondary outcomes

Identical regression analyses (as for the primary outcome) were run for the secondary outcome percentage of heavy drinking days.

Training effects on the time to first drink were analysed using Cox regression. Because the latter two secondary outcomes measure related constructs, these analyses were considered to test a family of hypotheses [41], and the critical alpha level in these analyses was adjusted by a Bonferroni correction (0.05/3 = 0.016, given three comparisons: two in the models on the percentage of heavy drinking days and one in the Cox regression). IAT data (d-score [40]) used repeated-measures analyses of covariance (ANCOVAs) in SPSS (version 22.0; IBM Corp, Armonk, NY, USA). Due to its non-normal distribution, GNG data (errors of commission) were analysed with analysis of variance (ANOVA)-type non-parametric statistics using the nparLD package in R [42]. As IAT and GNG assess disparate constructs and the related statistics contribute to a different conclusion, no adjustment for multiple testing was deemed appropriate.

[1]In addition to this main analysis, we also estimated the effect of the Alc-ITs on the percentage of days abstinent in a series of hierarchical linear models (see Supporting information, 2.3).

RESULTS

Participants and characteristics of treatment groups

An overview of socio-demographic and clinical variables for the main sample as well as for the three treatment groups (standard Alc-IT, *n* = 84; improved Alc-IT, *n* = 79; control, *n* = 79) is given in Table 2 (see also Supporting information, eTable 1, section 0). Of the total sample, 241 (99.5%) at baseline and 173 (71.5%) at 3-month follow-up provided complete TLFB data. The number of missing observations did not differ between treatment groups [control: *n* = 22 (27.8%), standard Alc-IT: *n* = 26 (30.9%), improved Alc-IT: *n* = 21 (26.6%); $P > 0.75$].

Primary outcome: percentage of days abstinent

Our main analysis,[2] a regression model describing the percentage of days abstinent at the 3-month follow-up as a function of the training intervention and the percentage of abstinence days at baseline (Table 3), yielded a significant effect of improved Alc-IT. Patients receiving improved Alc-IT reported an increase in days abstinent that was 11.48 percentage points (p.p.) higher than in the control condition (Figure 2, resulting in an estimated average of 85.78). Standard Alc-IT (estimated average of 70.95 percent days abstinent). showed no effect. An additional model indicated that there was no evidence for significant interactions between the daytime-of-training and the training intervention (Table 3) and including these variables in the regression model did not significantly improve the explained variance (Table 4). Of the evaluated potential covariates (age, gender, pharmacotherapy and length of residential treatment), none improved the explained variance (Table 4). An additional model indicated that there was no evidence for heterogeneity of the intervention effect across sites (all $P > 0.19$) and site was therefore not included as a random effect in the final analysis models.[3] An additional model directly comparing the two versions of Alc-IT against each other indicated a significantly higher increase in percentage of days abstinent in improved Alc-IT [$\beta = 14.84$, standard error (SE) = 4.35, confidence interval (CI) = 6.24–23.44, $P < 0.001$, adjusted $r^2 = 0.073$, Supporting information, 2.2.2].

Secondary outcomes

Percentage of heavy drinking days

No indicator for an effect of Alc-IT on the percentage of heavy drinking days at 3-month follow-up was detected, neither for improved Alc-IT nor for standard Alc-IT (Table 3). There was no indicator for an effect of one of the evaluated confounders or for an effect of study site (all $P > 0.12$).

Time to first drink

No significant differences were observed between the three intervention groups ($\chi^2_{(2)} = 2.47$, $P = 0.300$). On a merely descriptive level, survival analysis showed the highest probability to remain abstinent in improved Alc-IT, followed by standard Alc-IT and control condition.

Training effects on experimental tasks

GNG: Alcohol-related errors of commission decreased from pre- to post-training assessment [standard Alc-IT: pre: median (med) = 14, post: med = 11; improved Alc-IT: pre: med = 14, post: med = 10; control: pre: med = 14, post: med = 12]. A significant time × training group × picture-type interaction was observed (ANOVA-type statistics (ATS): $ATS_{(d.f.\ =\ 2)} = 11.07$, $P = 0.004$). Follow-up analyses in each training group yielded a significant time × picture-type interaction for improved Alc-IT ($ATS_{(d.f.\ =\ 1)} = 9.9$, $P = 0.002$), indicating that alcohol-related errors of commission decreased more strongly from pre- to post-training than neutral errors of commission. No such interaction was observed in the other two training groups (see Supporting information, 2.4).

IAT: No significant training effects on the d-score were observed ($F_{(d.f\ .=\ 2)} = 1.59$, $P = 0.21$, $\eta^2 = 0.015$).

DISCUSSION

This is the first study, to our knowledge, to investigate the effects of two different versions of an alcohol-specific inhibition training (Alc-IT) against a non-specific inhibition training in a clinical sample of patients with severe AUD. The primary outcome was the percentage of days abstinent at 3-month follow-up after discharge from residential treatment. We compared standard Alc-IT, a version in which half the trials were to be inhibited (including all alcohol-related stimuli), and a new improved Alc-IT, a version with a higher Go/NoGo ratio designed to place stronger demands on the inhibitory system, against a control condition consisting of a non-specific inhibition training. While no beneficial effects of standard Alc-IT on drinking outcomes were found, improved Alc-IT significantly increased the percentage of days abstinent at 3-month follow-up compared to the control training as well as compared to the standard Alc-IT.

The null result regarding standard Alc-IT is consistent with non-significant proof-of-principle studies in healthy volunteers [16,24,25], while at the same time questioning the generalizability of beneficial effects reported in other non-clinical studies [12–14] to clinical samples and longer follow-up periods. The improved Alc-IT was developed based on cognitive and neuroscientific research, indicating a

[2]Note that the supplementary analysis, hierarchical linear models, also yielded a significant effect of improved Alc-IT and no effect for standard Alc-IT (Supporting information, 2.3). Also, the sensitivity analyses based on alternative assumptions around missing data point in a similar direction (Supporting information, 2.2).

[3]As there was no evidence for potential effects related to study site, daytime of training or any of the tested potential confounders, those variables were not included in the final model.

TABLE 2 Baseline sample characteristics and descriptive measures of alcohol consumption

	Participant group											
	Total sample (N = 242)			Control (n = 79)			Standard Alc-IT (n = 84)			Improved Alc-IT (n = 79)		
Variable	M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range
Age (years)	44.76	9.70	22–60	44.53	9.88	24–60	44.98	9.53	23–60	44.76	9.83	22–60
Days in residential treatment	78.74	24.32	30–168	78.81	20.82	42–165	78.34	29.12	30–168	79.10	22.18	31–157
	n	%		*n*	%		*n*	%		*n*	%	
Gender												
Female	72	29.8		24	30.4		25	29.8		23	29.1	
Male	169	69.8		55	69.6		59	70.2		55	69.6	
LGBTQ	1	0.4		-			-			-		
Civil status												
Single	115	47.5		34	43		46	54.8		35	44.3	
Married	56	23.1		23	29.1		18	21.5		15	19	
Concubinage	2	0.8		-			-			2	2.5	
Divorced	65	26.9		20	25.3		20	23.8		25	31.6	
Widowed	4	1.7		2	2.5		-			2	2.5	
Pharmacotherapy												
No	215	93.1		73	91.2		75	94.9		67	93.1	
Yes	16	6.9		7	8.8		4	5.1		5	6.9	
	n	M	SD	*n*	M	SD	*n*	M	SD	*n*	M	SD
No. of prior detoxifications	148	3.70	4.12	46	4.15	4.50	55	3.27	4.07	47	3.74	3.81
AUDIT	237	26.12	6.39	76	26.80	6.10	82	25.63	6.88	79	25.96	6.16
AUD-S	238	26.62	8.94	79	27.47	8.16	83	25.61	9.53	76	26.85	9.05
BSCL GSI	238	0.78	0.60	79	0.71	0.48	80	0.82	0.70	79	0.82	0.60
OCDS	233	23.72	7.93	76	24.68	7.94	80	23.31	8.44	77	23.18	7.39
CAEQ	229	3.16	0.55	74	3.15	0.56	82	3.16	0.59	73	3.17	0.51
SOCTRATES	242	28.15	4.03	79	28.27	3.96	84	28.14	4.10	79	28.04	4.07
WHOQOL	227	3.31	0.51	75	3.34	0.51	75	3.30	0.52	77	3.28	0.52
Drinking outcome measurement												
PDA												
Baseline	241	24.73	29.34	79	25	29.46	83	24.6	30.7	79	24.58	28.13

(Continues)

TABLE 2 (Continued)

	n	M	SD	n	M	SD	n	M	SD	n	M	SD
3 m-FU	173	87.79	25.62	57	85.9	23.65	58	84.8	30.27	58	92.71	21.85
PHDD												
Baseline	241	70.72	31.94	79	71.7	31.31	83	68.7	34.68	79	71.81	29.77
3 m-FU	173	9.34	22.74	57	10.6	21.8	58	11.9	21.33	58	5.512	18.38
TTFD	156	59.26	36.31	49	55.1	36.76	52	55.3	39.07	55	66.71	32.47

Our statistical analyses on drinking outcome measurements were not based on means and standard deviations, but on regression estimates. However, the means of the TLFB-measurements are reported in the lower part of Table 2 for completeness and comparability with other studies. Standard Alc-IT = standard alcohol-specific inhibition training with an equiprobable ratio of Go and NoGo cues; improved Alc-IT = improved alcohol-specific inhibition training with a Go/NoGo ratio of 75/25; AUD-S = Alcohol Use Disorder Scale [35]; AUDIT = Alcohol Use Disorder Identification Test [45]; BSCL-GSI = general symptom index of the Brief Symptom checklist [46]; baseline = assessment in the 90 days prior to inpatient treatment; CAEQ = Comprehensive Alcohol Expectancy Questionnaire [47]; Control = control training; M = mean; OCDS = Obsessive–Compulsive Drinking scale [48]; PDA = percentage of days abstinent; PHDD = percentage of heavy drinking days; SOCRATES = Stages of Change Readiness and Treatment Eagerness Scale [49]; SD = standard deviation; TTFD = time to first drink in days after discharge from inpatient treatment; 3 m-FU = assessment 3 months after discharge from inpatient treatment; WHOQOL = WHO Quality of Life Scale [50].

deficiency in inhibiting pre-potent, dominant responses in AUD [20,37,43]. Since our trial started, one non-clinical study [15] tested a single session of such a variant in social drinkers, but did not observe effects on drinking outcomes. However, when we applied six inhibition training sessions in a clinical sample of patients with severe AUD, the improved version of Alc-IT resulted in considerable changes in post-treatment drinking behaviour. Besides an increased number of sessions and a higher motivation to change drinking behaviour in patients attending a residential treatment programme for AUD, this might also be due to baseline differences concerning alcohol-specific inhibition between the two populations (as observed in other types of cognitive bias modification [5,19]).

Although improved Alc-IT significantly increased the percentage of days abstinent it did not significantly affect the percentage of heavy drinking days, indicating that improved Alc-It might help to prevent patients from starting to drink, but not to limit drinking alcohol once started. Thus, improved Alc-It might be more helpful in the context of an abstinence-orientated treatment goal compared to controlled drinking programmes (which would be in line with other reports on effect of cognitive bias modification in AUD treatment [19]).

As potential working mechanisms of Alc-IT increased inhibitory control [21] and stimulus devaluation [22] have been proposed, both Alc-IT versions comprised the same number of pairings between alcohol and a stopping response, thus being identical in the characteristics relevant to stimulus devaluation. However, only the improved Alc-IT version with the more strenuous inhibitory component yielded beneficial effects. Thus, our pattern of results somewhat supported the inhibitory control enhancement hypothesis [at least as long as this hypothesis is refined in order to concern inhibition in the context of the relevant appetitive stimulus (i.e. alcohol in this case)] [44]. The experimental results also support this notion. In the IAT, a measure of stimulus evaluation, no devaluation effect could be detected (but note that a complementary measure of explicit devaluation was not assessed). In contrast, the GNG, which measures inhibitory control in an alcohol-related context, indicated that only in improved Alc-IT, alcohol-related errors of commission decreased more strongly than neutral errors of commission. This might be interpreted as improved Alc-IT strengthening alcohol-specific inhibitory control. As a potential limitation to this interpretation, this interaction effect in improved Alc-IT might also be driven by neutral errors of commission, not decreasing from pre- to post-training. In addition, when a direct statistical linkage between improvements in GNG and a change in drinking outcomes was assessed in a mediation analysis (Supporting information, 2.4.1), no statistical significance emerged. This might be due to either the sample size limiting statistical power or that such a mediation effect is truly not present in this sample, challenging the assumption of a working mechanism based on inhibitory control. However, the GNG data in the present study expand findings from proof-of-principle studies in healthy controls, most of which did not observe training effects on inhibitory measures [12,14,15,23]. Notably, however, none of these studies tested whether the Go/NoGo-based Alc-IT reduces errors of commission during a Go/NoGo-task, which are a

TABLE 3 Effect of standard and improved Alc-IT on the percentage of days abstinent and heavy drinking days

	Primary outcome: percentage of days abstinent							
	Training intervention model				Daytime of training model			
Effect	**Est**	**SE**	**95% CI**	**P**	**Est**	**SE**	**95% CI**	**P**
Intercept	74.30	3.58	67.25–81.35	<0.001	72.71	4.76	63.33–82.10	<0.001
PDA baseline	0.03	0.06	−0.10 to 0.15	0.663	0.03	0.06	−0.10 to 0.15	0.683
Standard Alc-IT versus control	−3.35	4.49	−12.20 to 5.50	0.457	−1.03	6.42	−13.67 to 11.62	0.873
Improved Alc-IT versus control	11.48	4.52	2.57–20.40	0.012	15.50	6.32	3.05–27.95	0.015
Daytime					3.38	6.51	−9.46 to 16.22	0.604
Standard Alc-IT × daytime					−4.73	9.13	−22.73 to 13.27	0.605
Improved Alc-IT × daytime					−8.36	9.11	−26.30 to 9.59	0.360
	Secondary outcome: percentage of heavy drinking days							
	Training intervention model				**Daytime of training model**			
	Est	**SE**	**95% CI**	**P**	**Est**	**SE**	**95% CI**	**P**
Intercept	15.53	3.87	7.91–23.15	<0.001	13.3	4.54	4.34–22.25	0.004
PHDD baseline	−0.03	0.04	−0.12 to 0.05	0.415	−0.04	0.04	−0.12 to 0.05	0.403
Standard Alc-IT versus control	2.1	3.27	−4.34 to 8.54	0.521	2.94	4.6	−6.12 to 11.99	0.523
Improved Alc-IT versus control	−4.77	3.56	−11.79 to 2.24	0.181	−7.52	4.79	−16.98 to 1.93	0.118
Daytime					4.78	4.81	−4.71 to 14.26	0.322
Standard Alc-IT × daytime					−1.96	6.53	−14.81 to 10.9	0.764
Improved Alc-IT × daytime					5.58	6.66	−7.53 to 18.7	0.402
N	242 patients							

Note that the final comparison model (the training intervention model) does not include interactions with possible confounding variables, with daytime of training or with study sites, because no evidence for effects of any of these variables was found. CI = confidence interval; Est = estimated regression coefficients; SE = standard error; improved Alc-IT = improved alcohol-specific inhibition training with a Go/NoGo ratio of 75/25; *n* = sample size; standard Alc-IT = standard alcohol-specific inhibition training with an equiprobable ratio of Go and NoGo trials; PDA = percentage of days abstinent; PHDD = percentage of heavy drinking days.

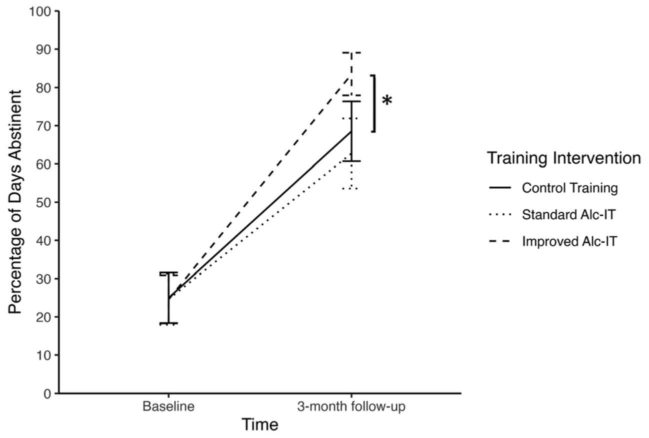

FIGURE 2 Training effects on primary outcome percentage of days abstinent at 3-month follow-up. Error bars represent standard error. Baseline = assessment at the beginning of residential treatment programme; 3-month follow-up = assessment 3 months after discharge from the residential treatment programme; standard Alc-IT = alcohol-specific inhibition training with a Go/NoGo ratio of 50/50; improved Alc-IT = alcohol-specific inhibition training with a Go/NoGo ratio of 75/25

TABLE 4 Overview of change in explained variance due to inclusion of additional variables

Variable	Δ var	*F*	*P*
Daytime	0.04	0.3	0.825
Clinic	0.02	0.69	0.66
Age	0.03	3.39	0.066
Gender	0.02	0.51	0.475
Pharmacotherapy	0.11	0.06	0.811
Days in res. treatment	0.02	1.64	0.2

Daytime = daytime of training as assigned during randomization; Δ var = relative increase in explained variance when this variable was added to the model; res. = residential.

typical measure of inhibitory control [20], and provide a highly proximal outcome of a Go/NoGo-based training. Furthermore, except for Smith *et al.* [15], all prior studies employed standard Alc-IT, for which the present study also did not observe effects. While differences in inhibitory assessment and in Go/NoGo ratio during Alc-IT might thus account for the differences between the present study and earlier, non-clinical studies, it is also conceivable that an inhibitory working mechanism is more relevant in a clinical sample [44].

From an experimental viewpoint, the equiprobable control condition might limit some conclusions regarding the working mechanism of the improved Alc-IT. Since the tailoring of the control condition was geared towards the more established variant (standard Alc-IT), it differed from the improved Alc-IT not only in the exclusive pairing of alcohol-stimuli with NoGo cues but also in the Go/NoGo ratio. Therefore, it cannot be excluded that a non-specific inhibition training with a high Go/NoGo ratio might have produced effects similar to those of improved Alc-IT. Future studies could include such a comparison and thereby determine whether the inhibitory working mechanism is actually an alcohol-specific one, operating in the context of motivationally relevant stimuli (for which improved Alc-IT was designed), or if it is rather a general inhibitory mechanism. As a limitation to generalizability, one has to keep in mind that improved Alc-It was administered in the context of a specialized inpatient treatment for AUD in a clinical sample of recently abstinent patients; thus, the effects might not be transferable to non-treatment-seeking individuals. Nevertheless, the present study provides important evidence for the efficacy of a new theory-based variation of Alc-IT as an add-on to relapse prevention treatment in a large clinical sample. Thus, our findings expand reports of positive effects of other computerized trainings, such as approach bias retraining [3–7], to a new form of training intervention.

In conclusion, our results indicate that alcohol-specific inhibition training can have a positive add-on effect in the treatment of AUD, but only when implemented with a high Go/NoGo ratio (75/25, the improved Alc-IT). Regarding the proposed working mechanisms, improved Alc-IT appears to work through inhibitory enhancement in the context of alcohol-related stimuli rather than stimulus devaluation. Altogether, the present study suggests that alcohol-specific inhibition training improves post-treatment drinking outcome in recently abstinent patients with AUD, and might serve as a cost-effective add-on intervention to specialized residential treatment programmes for AUD.

TRIAL REGISTRATION

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DECLARATION OF INTERESTS

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Maria Stein: Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Leila M. Soravia:** Conceptualization; funding acquisition; methodology; project administration; resources; supervision; validation; writing-original draft; writing-review and editing. **Raphaela M. Tschuemperlin:** Data curation; investigation; project administration; software; validation; writing-review and editing. **Hallie M. Batschelet:** Data curation; investigation; project administration; software; validation; writing-review and editing. **Joshua Jaeger:** Data curation; formal analysis; methodology; software; visualization; writing-original draft; writing-review and editing. **Susanne Roesner:** Resources; writing-review and editing. **Anne Keller:** Resources; writing-review and editing. **Juan Martin Gomez Penedo:** Formal analysis; methodology; supervision; writing-review and editing. **Reinout W. Wiers:** Methodology; supervision; writing-review and editing. **Franz Moggi:** Conceptualization; funding acquisition; methodology; project administration; resources; supervision; validation; writing-original draft; writing-review and editing.

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