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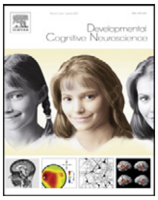

Approach bias modification in alcohol dependence: Do clinical effects replicate and for whom does it work best?

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ABSTRACT

Background: Alcoholism is a progressive neurocognitive developmental disorder. Recent evidence shows that computerized training interventions (Cognitive Bias Modification, CBM) can reverse some of these maladaptively changed neurocognitive processes. A first clinical study of a CBM, called alcohol-avoidance training, found that trained alcoholic patients showed less relapse at one-year follow-up than control patients. The present study tested the replication of this result, and questions about mediation and moderation.
Methods: 509 alcohol-dependent patients received treatment as usual (primarily Cognitive Behavior Therapy) inpatient treatment. Before and after treatment, the implicit approach bias was measured with the Alcohol Approach-Avoidance Task. Half of the patients were randomly assigned to CBM, the other half received treatment as usual only. Background variables, psychopathology and executive control were tested as possible moderating variables of CBM. One year after treatment, follow-up data about relapse were collected.
Results: The group receiving CBM developed alcohol-avoidance behavior and reported significantly lower relapse rates at one-year follow-up. Change in alcohol-approach bias mediated this effect. Moderation analyses demonstrated that older patients and patients with a strong approach-bias at pretest profited most from CBM.
Conclusions: CBM is a promising treatment add-on in alcohol addiction and may counter some of the maladaptive neurocognitive effects of long-term alcoholism.

1. Introduction

Alcoholism is a progressive neurocognitive disorder, in which premorbid vulnerability factors interact with neuroadaptations that result from excessive drinking (Koob and Volkow, 2010). For example, it has been argued that a strong reward response to alcohol, mediated by a neural circuitry involving the ventral striatum, may mediate initial binge-drinking and intoxication, while in later stages other mechanisms may play a crucial role, such as habits (with a transfer of activity from ventral to dorsal striatum, Everitt and Robbins, 2005), and withdrawal and negative affect driven drinking, with an important role for the extended amygdala (Koob and Le Moal, 2008; Koob and Volkow, 2010). In addition, lack of cognitive control over impulses has been implicated both as a risk factor for and as a consequence of addiction (Verdejo-García et al., 2008; De Wit, 2009), with increasing evidence indicating that the latter effect may be particularly strong when excessive substance use starts in adolescence (Crews and Boettiger, 2009; Meier

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et al., 2012). When taken together, these neuroadaptations in addiction may help to understand the difficulties many addicted people face when trying to quit their addiction. While recent research has emphasized the importance of the malleable adolescent brain in the early development of addiction (Crews and Boettiger, 2009; Casey and Jones, 2010; Gladwin et al., 2011), it should be noted that clinical patients are typically adult, with a large age-range. Hence, some of the later stages of addiction typically occur later in life, with its own developmental phases (Baltes et al., 1999). However, on a more positive note, it is important to realize that some of the neurocognitive abnormalities in addiction may reverse after prolonged abstinence (Fernandez-Serrano et al., 2011), and perhaps targeted training may help to achieve this goal (e.g., Alfonso et al., 2011).

While biomedical research on alcoholism has emphasized that addiction should be seen as a chronic brain disease (e.g., Leshner, 1997), this perspective should not lead to the conclusion that nothing can be done about addiction. In fact, many young people spontaneously mature out of alcoholism (Sher et al., 2005). And among the minority of more heavily addicted individuals who receive treatment, still a substantial minority does succeed in becoming long-term abstinent, aided by psychosocial treatment (Cutler and Fishbain, 2005), and in some cases medication (Heilig et al., 2011). Recently, in addition to traditional treatments, a novel set of training-paradigms have been developed, known as Cognitive Bias Modification (CBM). These have generated positive first results in the treatment of problem drinking in a community sample (Fadardi and Cox, 2009), and of alcoholism in patients (Schoenmakers et al., 2010; Wiers et al., 2011). These computerized interventions aim to directly change the relatively automatic or implicit cognitive motivational processes involved in addiction, of which patients may not always be aware and which are difficult to control and change by more traditional means. The present study focused on the re-training of one of these implicit processes: the automatically triggered action tendency to approach alcohol. Wiers et al. (2009b) developed the alcohol Approach-Avoidance Task (A-AAT) for assessment, and they later adapted it for re-training (Wiers et al., 2010b). The task asks participants to react with a joystick to pictures that appear on a computer screen. One category of pictures (e.g., pictures in landscape-format) requires an approach reaction (pull the joystick), whereas the other category (e.g., portrait-format pictures) requires an avoidance reaction (push the joystick, Rinck and Becker, 2007). Heavy drinking students showed an alcohol approach bias, reacting faster when alcohol pictures had to be pulled rather than pushed. This effect was the strongest for carriers of the OPRM1 G-allele, a gene also related to stronger alcohol-craving (Wiers et al., 2009b). In a subsequent study, the A-AAT was adapted as a training tool, demanding a pull movement in response to alcohol pictures in 90% of the trials (approach-training) or demanding a push movement in 90% of the trials (avoidance-training). Heavy drinking students who were successfully re-trained to avoid alcohol showed significantly less alcohol intake in a subsequent taste-test, compared to heavy drinkers trained to approach alcohol, without reporting any awareness of the training contingency (Wiers et al., 2010).

In a subsequent first clinical study on the effects of this novel variety of CBM, Wiers et al. (2011) tested the effects of four sessions of A-AAT avoidance training in alcohol-dependent patients in an inpatient setting. After alcohol-avoidance training, patients' alcohol-approach bias changed into an alcohol-avoidance bias, which generalized to untrained pictures in the same task (close generalization). Further generalization was found in an entirely different task requiring categorization of words, in one phase alcohol-words with approach-words, in another alcohol-words with avoidance words (an Approach-Avoid Implicit Association Task). Moreover, patients in the training group showed 13% less relapse one year after treatment discharge, compared to patients in the control group, who had received either sham training or no training (note that all patients received an average of 3 months of treatment as usual, primarily cognitive behavioral therapy).

So far, little is known about predictors of successful training. On the basis of cognitive (e.g., Wiers and Stacy, 2006) and neurocognitive (e.g., Bechara, 2005) dual-process models, a number of studies found that implicit cognitive processes are a better predictor of alcohol use in people with relatively weak executive control (EC) capacities (Grenard et al., 2008; Houben and Wiers, 2009; Thush et al., 2008), and one recent study found that EC moderates the relation between alcohol-approach tendencies and drinking behavior in high-risk adolescents (Peeters et al., 2012). In addition to moderating prediction, EC may also moderate training effects, with stronger training effects (in anxiety) in participants with relatively weak EC (Salemink and Wiers, 2012). The reasoning is that in treatment, either control over the maladaptive impulse has to increase, or the impulse itself has to be changed. While all of these studies concerned non-clinical young groups, one can conclude from these findings that approach-bias re-training might work especially well for patients with relatively weak EC capacities. Therefore, we used the classical Stroop color-word interference task (Stroop, 1935) as a potential moderator (as in Houben and Wiers, 2009; Peeters et al., 2012; Salemink and Wiers, 2012; Wiers et al., 2009a). It has been found that the task activates fronto-limbic circuits, including the dorsolateral prefrontal cortex and the anterior cingulated cortex (Brewer et al., 2008; Liu et al., 2008). Deviant brain activation during a classical Stroop task has been associated with risk for addiction, both in adolescents with a family history of alcoholism (Silveri et al., 2011), and in children with attention deficit hyperactivity disorder when they are off medication (Brewer et al., 2008). Moreover, reduced brain activation during a Stroop task has also been associated with aging (Li et al., 2009; Mohtasib et al., 2012), and with treatment response in (cocaine) addiction (Brewer et al., 2008).

In summary, the present study had two main objectives: First, to test whether the effect of adding computerized approach-bias re-training to cognitive behavioral treatment increases abstinence in alcoholic inpatients (replicating Wiers et al., 2011) and whether the effect on treatment outcome would be mediated by the amount of change in approach-bias. The second aim was to investigate whether success of training could be predicted by patients' level of EC and/or background variables.

2. Methods

2.1. Participants

Participants were 509 alcohol-dependent patients administered to a three-months inpatient treatment in the salus clinic, Lindow. The mean age was 46 years, with a range from 19 to 79 (SD = 9). Patients were informed about the study and their option to withdraw from it, which would not cause them any disadvantages regarding their treatment. Included patients signed informed consent. The study was approved by the ethics committee of the German Pension Fund, which finances the treatment of alcohol dependence in rehabilitation clinics. We included every patient with a primary alcohol dependency diagnosis, assessed with the computerized version of the Composite International Diagnostic Interview, CIDI (Saunders et al., 1993). Exclusion criteria were neuro-cognitive problems (3 patients), strong withdrawal symptoms (1 patient), history of schizophrenia (3 patients), and visual or hand-motoric handicaps (4 patients). Patients with severe neurological disorders such as Korsakoff-syndrome are not admitted to the salus Clinic. None of the patients received anti-craving medication. Eleven patients dropped out at/after pretest and 13 patients had to be excluded due to technical issues of the computer program. The final analytical sample therefore consisted of 475 patients (without overlap with the previous study, Wiers et al., 2011).

2.2. Assessment and outcome measures

At intake, patients were diagnosed using the computerized version of the CIDI, which was complemented by a diagnostic interview based on the German manual for documentation in addiction help (Fachverband, 2010), including information on the amount of alcohol per drinking occasion and the duration of alcohol problems. Both the CIDI and the interview were the basis for the final expert ratings on diagnoses, made by clinical psychologists. The Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1989), the Alcohol Abstinence Self-Efficacy Scale (AASE; DiClemente et al., 1994), Beck's Depression Inventory (BDI; Beck and Steer, 1987; Hautzinger et al., 1994) and the Symptom Check List, SCL-90 (Derogatis, 1986; Franke, 1995) were also administered.

2.3. Experimental task

2.3.1. Alcohol-AAT (Approach-Avoidance Task)

The Alcohol AAT (Wiers et al., 2009b) measures the automatic approach tendency toward alcohol. Participants were asked to react to the format of pictures using a joystick (push landscape pictures, pull portrait pictures), ignoring the contents of the pictures. We used two categories of pictures – 20 different alcoholic beverages and 20 different soft-drinks. Every picture appeared both in landscape and in portrait format. They were presented one by one and appeared in a quasi-random order (maximum three consecutive pictures of the same category or format). Pushing a picture away went along with a decrease in picture size, whereas pulling a picture closer resulted in an increased size (zoom-effect). The task started with 10 practice trials showing neutral objects. The practice trials were followed by 160 test trials. This test was administered at both pre- and post-test.

2.3.2. Alcohol-AAT (Approach-Avoidance Task)–Training Version (Wiers et al., 2010b)

For CBM, we used the A-AAT as just described. The training effect was achieved by presenting alcohol pictures in the push-away format only and soft-drink pictures in the pull-closer format only.

2.3.3. Color Stroop (EC)

We used a variety of the Color Stroop task (Stroop, 1935) as it was used by Stetter et al. (1994) to assess the strength of inhibitory EC in alcohol-dependent patients. Names of colors were presented in different ink colors in the middle of the computer screen. Participants were to decide whether ink color and printed color were the same, giving their answer by pushing marked keys for "same" vs. "different" on the keyboard. The test consisted of 48 practice-trials and 48 test-trials. This test was only administered during the pretest.

2.4. Questionnaires

2.4.1. Beck Depression Inventory (BDI)

The BDI (Beck and Steer, 1987; German version Hautzinger et al., 1994) was used to measure the severity of depressive symptoms. Internal consistency (alpha = .8) and test–retest reliability (r = .92) are high (Beck and Steer, 1987).

2.4.2. Rosenberg Self-Esteem Scale (RSES)

The RSES (Rosenberg, 1965; German version by Collani and Herzberg, 2003) is a 10-item self-report scale that addresses feelings of global self-worth. All responses are made on a scale ranging from 1 (strongly disagree) to 6 (strongly agree). It shows a reasonable test–retest reliability of r = .87 (Bosson et al., 2000).

2.4.3. Symptom Checklist 90-R (SCL90-R)

The SCL-90-R (Derogatis, 1986; Franke, 1995) measures the physical and psychological impairment of a person within the past seven days. It consists of 90 questions, rated on a five-point Likert scale. Answers add up to nine scales. We used the Global Severity Index as a possible predictor; it is the sum score of the SCL90-R, indicating the general level of distress. Internal consistency for the nine subscales ranges from Cronbach's α of .78 to .90, while Cronbach's α for the Global Severity Index is .97 (Schmitz et al., 2000).

2.4.4. Alcohol Abstinence Self Efficacy Scale (AASE)

The AASE (Bott et al., 2003; DiClemente et al., 1994) assesses patients' confidence to stay abstinent in 20 different situations as well as their temptation to drink in these situations. Participants are asked to give a current estimate of temptation and self-efficacy on a five-point Likert scale. Internal consistency is rather high for both subscores, reaching from Cronbach's $\alpha = .95$ (efficacy) to Cronbach's $\alpha = .97$ (temptation) (DiClemente et al., 1994).

2.4.5. Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT (Babor et al., 1989) is a screening instrument for problematic alcohol consumption, constructed by the WHO. It consists of 10 questions on drinking amount, frequency and negative consequences. Test–retest reliability in a German population was high, $r = .95$ (Dybek et al., 2006).

2.5. Conditions and experimental manipulation

Patients were randomly assigned to one of the two groups (training vs. no training). Patients in the experimental training group were trained in 12 sessions to respond with an avoidance movement (push) to alcohol pictures and with an approach movement (pull) to non-alcoholic drinks. This was achieved by presenting all alcohol pictures in landscape format and all soft-drink pictures in portrait format. The instruction remained the same (push landscape pictures, pull portrait pictures). During training, participants had to correct errors. Two hundred training trials per session were presented with a short break halfway. Each training session took approximately 15 min and started with a short A-AAT assessment (same as pretest) to measure training effects of the previous session (a detailed analysis of the training effects is beyond the scope of the present paper). Patients in the control group received no training at all instead of a sham-training, because we had found no significant difference between no-training and sham-training in a previous study (Wiers et al., 2011).

2.6. Procedure, study design, data analysis

Within the first week of therapy (diagnostic phase), patients took part in a "neuropsychological checkup" including the A-AAT. The described questionnaires (BDI, SCL90-R, AASE, AUDIT) were also filled out, within the diagnostic phase. After the pretest, patients were randomly assigned to training conditions (training vs. no training). Participants assigned to the training group started the 12 training sessions six weeks before their planned discharge, to ensure a standardized amount of time between the last training session and discharge. Along with the experimental manipulation, patients received treatment as usual, which consisted of abstinence-orientated inpatient CBT-based treatment, including both individual and group sessions, for an average of 3 months (Schmidt et al., 2006), following all standards of the guidelines of the German Addiction Society and the study by Wiers et al. (2011). The average treatment duration was 81 days (range 27–125 days). Treatment duration did not differ between training groups. One year after discharge, patients received a standard follow-up questionnaire asking about alcohol consumption since treatment. Participants who did not return the questionnaire were reminded by post twice and finally called by phone. In some cases (e.g., death) information was retrieved from relatives or physicians.

The main outcome variable was treatment outcome at one-year follow-up. The one-year follow-up was analyzed using a binary outcome variable (successful outcome or not), following conservative Intention-To-Treat (ITT) principles. Following the protocol DGSS-4 of the German Addiction Society (as in Wiers et al., 2011), successful outcomes were (1) either no relapse at all or (2) a single lapse shorter than 3 days, ended by the patient without further negative consequences. No success was defined as relapse or death, "no information", or refusal (ITT).

To predict who will profit from the training, the predictive value of the implicit measure (A-AAT) and the questionnaires (AUDIT, AASE, SCL-90, BDI), as well as the demographic facts (age, years of alcohol dependence, amount of alcohol per drinking situation), and the measure of EC (Stroop task) were of interest. Greenwald and colleagues have developed an improved scoring-algorithm for another reaction time (RT) test of associative processes, the Implicit Association Test, which standardizes the difference in response latencies by dividing an individual's difference in RTs by a personalized standard deviation of these latencies (Greenwald et al., 2003; Sriram et al., 2010). The advantage of such standardized scores over simple difference scores is that they are less vulnerable to biases due to differences in average RT. In the study by Wiers et al. (2011), the algorithm also did better than the original scoring algorithm with the A-AAT, therefore we use it here again. The algorithm yields an approach bias score for each patient, for each combination of test time (pre, post) and drink type (alcohol, soft-drink). Positive scores indicate an approach tendency, negative ones an avoidance tendency. The larger the score, the stronger the approach tendency.

The analytical sample for the A-AAT pretest was 406. Sixty-nine additional patients were excluded, also from the A-AAT posttest, due to excessive errors (>35%) in the A-AAT pretest (35 in the training group and 34 in the control group). Of the 406 remaining participants, for the A-AAT posttest the analytical sample included 341 patients, with 65 scores missing due to excessive errors or dropouts (25 training group, 40 control group). Analytical samples for the other tests were: 470 for the BDI (2 trained and 3 controls missing); 466 for the SCL-90 (5 trained and 4 controls missing); 461 for the AUDIT (7 trained and 7 controls missing); and 424 for the AASE-Craving (24 trained and 27 controls missing); and 388 for the AASE-Self-Efficacy (63 trained and 24 controls missing).

3. Results

3.1. AAT training effects

Training effects on the approach-bias scores were analyzed with a 2 (Time: pretest/posttest) × 2 (Drink-type: alcohol/soft-drinks) × 2 (Training: experimental/control) mixed ANOVA. There were main effects of Time, $F(1,350) = 21.6$, $p < .001$, $\eta_p^2 = .06$, and Drink-type, $F(1,350) = 145.7$, $p < .001$, $\eta_p^2 = .29$, an interaction effect between Drink-type and Training, $F(1,350) = 26.5$, $p < .001$, $\eta_p^2 = .070$ and a three-way interaction between Drink-type, Training and Time, $F(1,350) = 12.2$, $p = .001$, $\eta_p^2 = .03$.

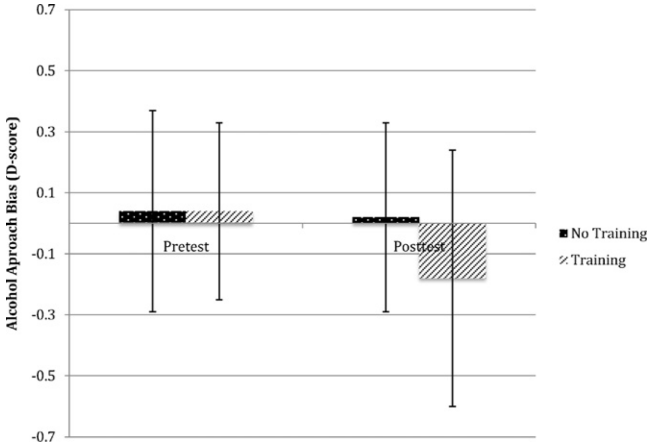

Fig. 1. *D* scores for soda pictures on the alcohol approach/avoidance task for participants in the two groups (experimental and control). *D* scores were derived at pretest and posttest from the difference between mean response latencies for avoidance movements to pictures (pushing a joystick) and approach movements to picture (pulling a joystick); a positive value indicates an approach bias, and a negative value indicates an avoidance bias. Error bars indicate ±1 SD.

When analyzing alcoholic drinks and soft-drinks separately, in the case of alcohol, there was a significant main effect of Time, $F(1,350) = 22.3$, $p < .001$, $\eta_p^2 = .06$, and a significant interaction between Time and Training, $F(1,350) = 23.3$, $p < .001$, $\eta_p^2 = .06$. For soft-drinks, there was also a significant main effect of time, $F(1,350) = 8.4$, $p = .004$, $\eta_p^2 = .02$, but no Time × Training interaction. As can be seen in Fig. 1, patients did not show a significant approach or avoidance bias for alcohol at pretest, indicating that they were most likely ambivalent (both approach and avoidance associations triggered, cf. Wiers et al., 2011). Only patients of the training group showed a significant alcohol avoidance bias at posttest, while the control group did not develop a significant alcohol avoidance bias. For soft-drinks, both groups kept a strong approach bias over time (see Fig. 2).

3.2. Clinical outcomes

The analyses reported below were run twice, once with an ITT-defined training group (including patients with incomplete training sessions), and once including only patients with complete training (ten or more sessions), because incomplete training sessions may indicate relapse during treatment.

We reached 74.9% of the patients for the one-year follow-up. In the training group, 51.2% (127/248) of the patients were classified as successful (abstinent or single lapse shorter than 3 days), whereas in the control group, only 42.7% (97/227) of the patients were classified as successful. This difference was significant, $\chi^2(1) = 3.42$, $p = .039$; $\eta_p^2 = .085$ (tested one-sided, given that we replicate an expected outcome). Limiting the training group to

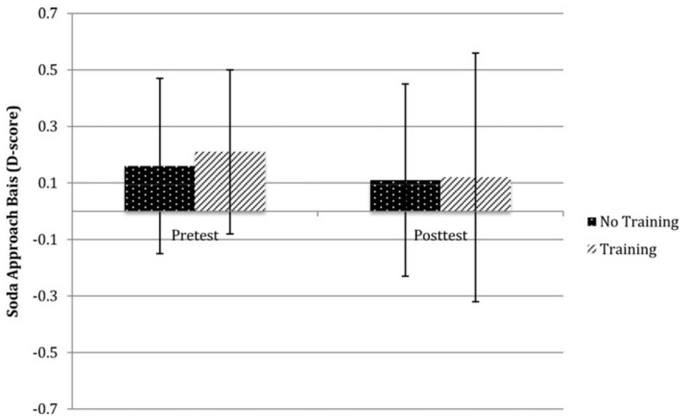

Fig. 2. *D* scores for soda pictures on the alcohol approach/avoidance task for participants in the two groups (experimental and control). *D* scores were derived at pretest and posttest from the difference between mean response latencies for avoidance movements to pictures (pushing a joystick) and approach movements to pictures (pulling a joystick), a positive value indicates an approach bias, and a negative value indicates an avoidance bias. Error bars indicate ±1 SD.

Table 1
Logistic regression of clinical outcome.

Variable	b	SE b	Wald z	p
Age	−0.358 (−0.353)	0.126 (0.123)	3.224 (8.24)	0.004 (0.004)
Training condition	−0.676 (−0.648)	0.229 (0.224)	8.711 (8.383)	0.003 (0.004)
BDI	0.219 (0.202)	0.156 (0.153)	1.964 (1.741)	0.161 (0.187)
Number of previous detoxifications	0.342 (0.329)	0.141 (0.134)	5.572 (6.053)	0.015 (0.014)
Gender	−0.497 (−0.565)	0.277 (0.273)	3.224 (4.287)	0.073 (0.038)
Audit	0.179 (0.166)	0.120 (0.117)	2.247 (2.028)	0.134 (0.154)
Dependence in years	−0.076 (−0.085)	0.120 (0.118)	0.398 (0.52)	0.595 (0.471)
Treatment duration	0.027 (0.054)	0.121 (0.119)	0.049 (0.209)	0.825 (0.647)
SCL90	0.109 (0.122)	0.157 (0.154)	0.486 (0.63)	0.486 (0.428)

Note: AUDIT: Alcohol Use Disorder Test (Saunders et al., 1993); BDI: Beck Depression Inventory (Hautzinger et al., 1994); SCL 90: Symptom Checklist 90 (Franke, 1995). Results for ITT analyses are presented in brakets.

Table 2
Logistic Regression of training success, predictor: age.

Variable	b	SE b	Wald z	p
Training condition	0.080 (0.091)	0.310 (0.3)	0.067 (0.092)	0.796 (0.762)
Age Group	−0.159 (−0.159)	0.161 (0.161)	0.975 (0.975)	0.324 (0.324)
Age Group × Training Condition	−0.479 (−0.479)	0.238 (0.233)	4.053 (4.217)	0.044 (0.4)

Note: Results for ITT analyses are presented in brakets.

patients with complete training, results were as follows: 54.9% (118/227) of patients in the training group and 45.1% (97/227) of patients without training were classified as success. This difference was also significant, $\chi^2(1) = 3.896$, $p = .03$; $\eta_p^2 = .093$ (tested one-sided). Note that when we analyzed only responding patients (deviating from the DGSS-4 protocol), the difference was no longer significant ($p = .21$ for patients with complete training, $p = .18$ for ITT analyses). In the following analyses, we report results for the training group with complete training. ITT analyses are reported in footnotes only when the pattern of significance deviates.

3.3. Moderation of clinical treatment outcome

In line with the analyses of Wiers et al. (2011), we analyzed a number of variables, which could potentially explain differences in abstinence rates, using logistic regression. Information on the severity and duration of the addiction (AUDIT score, duration of alcohol dependence, treatment duration, number of previous detoxifications) as well as information on gender, age, psychopathology (BDI, SCL-90) and training group were included in a logistic regression. In combination with these variables, the training group still remained a significant predictor of abstinence. Additional significant predictors were age and the number of previous detoxifications (see Table 1). Taking part in the training, being older, and having experienced fewer previous detoxifications were all associated with a lower risk of relapse (Table 1).[1]

3.4. Prediction of successful training

Taking part in the training increases the likelihood to remain abstinent, but not every single patient may profit from it. Therefore, our second aim was to determine who would profit most from the CBM training. We analyzed this with logistic regression, with the potential predictive variables concerning the severity of alcoholism (AUDIT, AASE, duration of alcohol problems, number of previous detoxifications, amount of alcohol per drinking occasion), psychopathology (SCL-90, BDI) Self-Esteem (RSES), demographics (age, gender), and cognitive tasks of the pretest (A-AAT, Color Stroop), to predict treatment outcome. For all variables, we created three equally large groups (low, medium, high) and analyzed the predictive power of their interaction with training group (training vs. control) on the treatment outcome (one year follow-up). Significant effects were only found for age × training, indicating that older patients profited most from the A-AAT training (Table 2).

[1] For ITT analyses, age, gender, and the number of previous detoxifications were significant predictors in addition to the training condition. Being older, being female, and having had fewer previous detoxifications were all associated with less relapse (identical, except for the additional prediction of gender).

Table 3
Logistic regression of clinical outcome including the change in bias as predictor.

Variable	*b*	SE *b*	Wald *z*	*p*
Age	−0.374	0.143	6.829	0.009
	(−.369)	(.140)	(6.977)	(0.008)
Training condition	−0.453	0.273	2.751	0.097
	(−0.419)	(0.268)	(2.455)	(0.117)
BDI	0.288	0.176	2.667	0.102
	(0.274)	(0.173)	(2.513)	(0.113)
Number of previous detoxifications	0.400	0.163	6.050	0.014
	(0.382)	(0.152)	(6.354)	(0.012)
Gender	−0.498	0.316	2.479	0.115
	(−0.577)	(0.311)	(3.433)	(0.064)
Audit	0.247	0.132	3.511	0.061
	(0.226)	(0.128)	(3.101)	(0.078)
Dependence in years	−0.052	0.145	0.128	0.721
	(−0.075)	(0.142)	(0.276)	(0.599)
Treatment duration	0.049	0.146	0.115	0.735
	(0.064)	(0.143)	(0.199)	(0.655)
SCL90	0.076	0.171	0.195	0.659
	(0.1)	(0.169)	(0.350)	(0.554)
Change in bias	0.579	0.299	0.376	0.023
	(0.639)	(0.293)	(4.754)	(0.029)

Note: AUDIT: Alcohol Use Disorder Test (Saunders et al., 1993); BDI: Beck Depression Inventory (Hautzinger et al., 1994); SCL 90: Symptom Checklist 90 (Franke, 1995). Results for ITT analyses are presented in brakets.

3.5. Mediation by change in alcohol approach bias

We hypothesized that the change in alcohol approach bias, being the target of the A-AAT training, would mediate treatment outcome, with a larger change predicting abstinence. In accordance with the mediation model of MacKinnon et al. (1995), we analyzed three different pathways of predictive power. Path “a”: Training condition predicted change in alcohol approach bias, analyzed by linear regression, $B = -.230$ (.05), $p < .001$. Path “b”: Change in alcohol approach bias predicted treatment outcome analyzed by logistic regression, $B = .570$ (.112), $p = .014$. Path “c”: Training condition predicted treatment outcome, $B = -.372$ (.189), $p = .049$, analyzed by logistic regression. For ITT analyses results were as follows: path a: $B = -.231$ (.049), $p < .001$; path b: $B = .599$ (.227), $p = .008$; path c: $B = -.341$ (.185), $p = .065$.

Entering both the training condition and the change in alcohol approach bias as predictors for treatment outcome into the logistic regression, we calculated the adjusted effect of the training condition (path c’), which turned out to be no longer significant ($p = .748$, for ITT: $p = .821$), whereas the change in bias remained significant, $B = .550$ (.238), $p = .021$ (for ITT: $B = .586$ (.233), $p = .012$). We then added the change in alcohol approach bias to the moderation model of treatment outcome (see above). Significant predictors were the number of previous detoxifications, $B = .400$ (.163), $p = .014$ (for ITT: $B = .382$ (.152), $p = .012$), and age, $B = -.374$ (.143), $p = .009$ (for ITT: $B = -.369$ (.140), $p = .008$) and the change in alcohol approach bias, $B = .579$ (.229), $p = .023$ (for ITT: $B = .639$ (.293), $p = .029$). Training condition was no longer significant ($p = .097$, for ITT: $p = .117$) (see Table 3 and Fig. 3). These results support the hypothesis of a mediation effect. In line with recommendations of MacKinnon et al. (2007), we used the RMediation program to calculate confidence intervals for the mediation effect. This procedure accounts for non-normal distributions of the indirect a–b path, by constructing asymmetric confidence intervals. The 95% confidence interval reached from −.273 to −.026 (for ITT: −.271 to −.0.032). Since this does not include zero, the mediation effect is statistically significant (Fig. 3 and Table 3).

3.6. Moderation of change in alcohol approach bias

Given the observed significant mediation by the change in alcohol-approach bias, we further analyzed moderators of this change by multiple regression analyses. In addition to the variables of the previous moderation analyses, we now included the A-AAT pretest scores, and the Stroop score as a measure of EC. Significant predictors were the A-AAT pretest score ($p < .001$) and the duration of treatment ($p = .005$). The Stroop score turned out not to be significant ($p = .665$). A strong alcohol approach tendency and a longer time in therapy were associated with a stronger change in bias. EC (Stroop score) was not found to moderate the effect on change in approach bias (Tables 4 and 5).

4. Discussion

The main findings of the present study were first that we replicated the effects of a computerized alcohol-avoidance training, both on the process trained (alcohol-avoidance tendencies were created in the trained group only) and on long-term clinical outcomes (abstinence rates at follow-up), after controlling for background variables. Second, this long-term effect was mediated by the change in alcohol-approach tendencies from pre- to post-test, which had not been significant in our first clinical study (Wiers et al., 2011). Third, regarding moderators, the strength of alcohol-approach tendencies at pretest, but not the

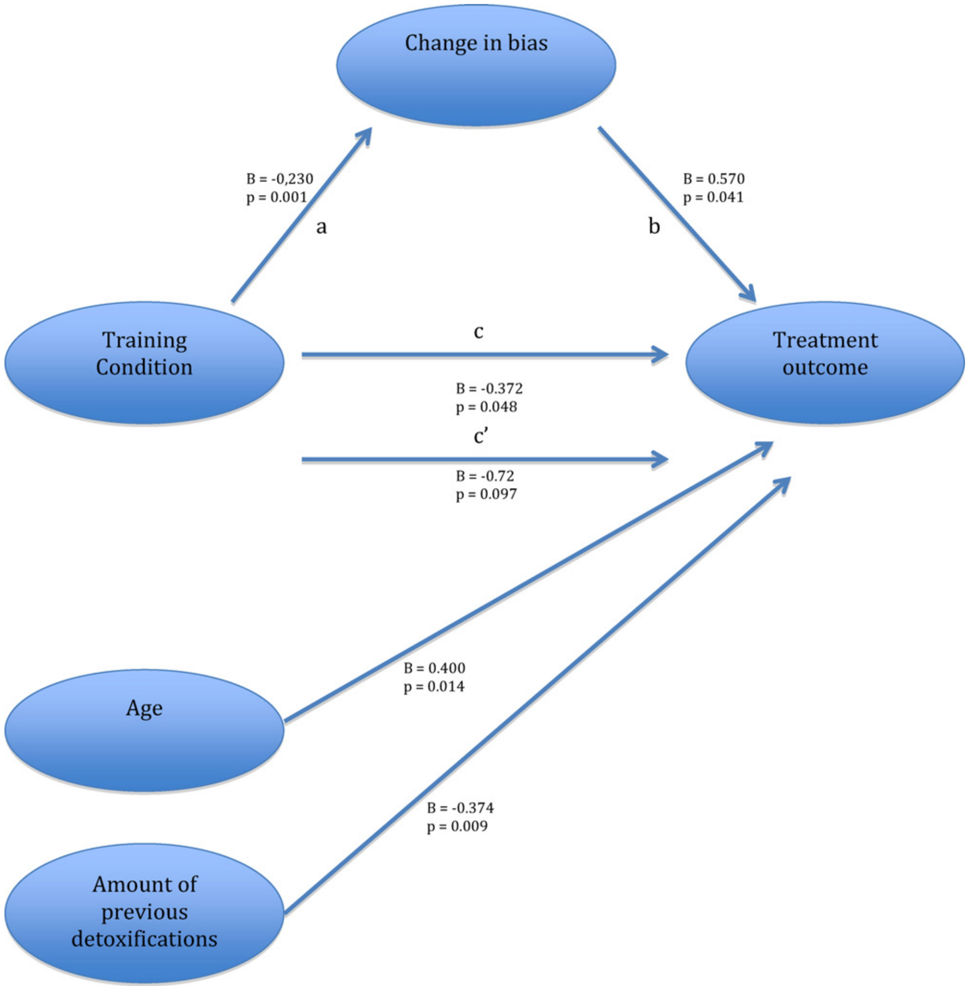

Fig. 3. Mediation of treatment outcome.

hypothesized weakness of EC predicted the amount of change in approach-tendencies, and age significantly predicted who would profit most from the training. We did not find an overall alcohol approach bias before treatment.

First, the clinical effects of the CBM training on both short-term effects (increase of alcohol avoidance tendencies over time in therapy) and long-term effects (abstinence rates after a year) were replicated. This strengthens the suggestion to add this variety of CBM to treatment as

Table 4
Moderation of change in alcohol approach bias.

Variable	*b*	*t*	*p*
Number of previous detoxification	0.023	0.809	0.419
BDI	−0.042	−1.233	0.219
Age	−0.013	−0.494	0.622
Condition	−0.1	−1.938	0.054
Duration of treatment	0.079	2.851	0.005
Audit	−0.024	−0.959	0.339
Gender	−0.036	−0.623	0.534
Dependence in years	−0.015	−0.503	0.616
SCL90	0.019	0.611	0.542
Stroop score	−0.012	−0.433	0.665
A-AAT pretest	−0.912	−10.64	0.000

Note: AUDIT: Alcohol Use Disorder Test (Saunders et al., 1993); BDI: Beck Depression Inventory (Hautzinger et al., 1994); SCL 90: Symptom Checklist 90 (Franke, 1995).

Table 5
Correlation of predictors.

	Training condition	Age	Number of previous detoxification	Duration of alcohol problems	Amount of alcohol per drinking occasion	BDI	SCL-90	Audit	AASE craving	AASE self-efficacy	Alcohol Approach tendency pretest	Executive control (stroop)	RSES Pretest
Age	−0.011												
Number of previous detoxification	0.063	0.008											
Duration of acohol problems	−0.020	0.244**	0.203**										
Amount of alcohol per drinking occasion	0.058	0.149**	0.314**	0.158**									
BDI	0.091	−0.065	0.093	0.026	0.105*								
SCL-90	0.061	−0.082	0.064	0.019	0.125**	0.308**							
Audit	−0.0061	−0.143**	0.021	0.021	0.232**	0.633**	0.308**						
AASE craving	0.009	−0.177**	0.069	0.063	0.094	0.372**	0.435**	0.280**					
AASE self-efficacy	−0.042	0.032	−0.102	−0.08	−0.026	−0.327**	−0.338**	−0.115*	−0.614**				
Alcohol Approach tendency pretest	−0.053	0.198	0.005	−0.009	−0.023	−0.038	0.045	0.030	0.049	−0.127*			
Executive control (color stroop)	0.053	0.207**	−0–018	0.043	−0.075	−0.077	−0.101	−0.041	−0.042	0.030	0.051		
RSES Pretest	0.063	0.059	0.059	−0.1	−0.009	−0.564**	−0.413**	−0.113*	−0.295**	0.238**	0.019	0.090	

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

usual, to supplement the treatment of addictive disorders. The short-term effects were mainly due to the experimental group developing a strong alcohol avoidance bias, whereas no change in bias for soft-drinks occurred. For the control group, there was no change in bias for either alcohol or soft-drinks. These findings also replicate the first clinical study of alcohol-avoidance training, in which we found that avoidance training was successful in producing an alcohol-avoidance bias, while no-training or sham-training were not (Wiers et al., 2011). Note that, even though the theoretical background of CBM is based on the assumption of an alcohol approach bias, we did not find a clear overall approach bias for alcohol in alcohol-dependent patients, neither in this study nor in the previous one (Wiers et al., 2011). This is in line with a study by Barkby et al. (2012), who found no differences in approach bias between alcohol-dependent patients and controls. This may be due to ambivalence because patients hold both approach and avoidance associations toward alcohol (McEvoy et al., 2004; Wiers et al., 2006). Long-term alcohol-dependent patients are most likely to feel both approach impulses due to the negative reinforcement effect of alcohol (reducing withdrawal) and avoidance impulses, due to awareness of negative long-term effects of drinking (e.g., losing job, partner, health outcomes, etc., Jones and McMahon, 1998). Despite awareness of long-term negative outcomes, salient situational cues may still trigger approach-tendencies in a patient in a risky situation after leaving the clinic. Therefore, CBM could reduce ambivalence by strengthening avoidance impulses, weakening approach tendencies, and/or control over these tendencies (cf. Gladwin et al., 2011). A related interesting finding was that the trained patients' approach bias for soft-drinks did not increase, even though they approached soft-drinks as frequently as they avoided alcohol throughout the training. This may indicate that it is easier to influence ambivalent action tendencies than to make already existing tendencies even stronger. Further research is needed to investigate these suggestions.

Regarding long-term effects, fewer relapses occurred in the training group, and the training condition remained a significant predictor of treatment outcome, even when other significant predictors were added to the model. Note that results were no longer significant when excluding missing data on the one year follow-up. One could argue that the training only increased patients' willingness to answer follow-up questionnaires, maybe because they liked the training and held positive memories of their stay in the clinic (social desirability). However, we did not find increased return rates in the sham-training condition of our previous study (Wiers et al., 2011). Further, the fact that the change in cognitive bias mediated treatment outcome makes this alternative explanation highly unlikely. It seems more likely that the lack of significance is due to a response bias indicating that patients are more likely to answer if they are still abstinent. Yet to diminish this artifact, further research should reconsider using sham training instead of a no training condition, since this should decrease possible effects of social desirability.

In contradiction to our finding of increased abstinence after alcohol avoidance training, a recent study by Spruyt et al. (in press) suggested that an avoidance bias might be harmful for patients, increasing their risk of relapse. However, there are two important differences with the current study. First, Spruyt et al. used the Stimulus Response Compatibility (SRC) task to measure approach-avoidance tendencies with a symbolic movement of a manikin toward or away from alcohol. Importantly, this is a structurally different task from the AAT used here. The SRC version used by Spruyt et al. is a relevant-feature task, it requires participants to categorize stimuli with respect to the relevant stimulus characteristics (approach alcohol in one block, avoid alcohol in another block), while the AAT version used here is an irrelevant feature task, in which participants react to the format of the picture, unrelated to the contents (cf., De Houwer, 2003). A relevant feature task involves strong EC, as a recent neurocognitive study indicated (Cousijn et al., 2012). Also, the SRC and AAT are not correlated. Hence, an avoidance bias at the SRC cannot be used to predict training outcomes with the AAT, while an approach bias in the AAT can at the group-level (as we demonstrated here), although not at the individual level.

Second, Spruyt et al. (in press) further argued that so far, it was unclear whether changes in approach bias are directly related to the improvement of trained patients. Indeed, in our previous study we failed to find mediation by the change in alcohol-approach tendencies on treatment outcome. The present replication study included twice as many patients, and indeed found that the clinical effect was mediated by the change in alcohol-approach bias. Most likely, this is due to increased statistical power, and it supports the hypothesis that an automatic alcohol-approach bias can be modified by CBM, and that this modification is the core aspect of CBM which actually leads to a valuable, clinically relevant increase of abstinence rates.

Regarding moderation, the amount of change in alcohol-approach bias was moderated by the A-AAT prescore. A recent study in the domain of anxiety also found the strongest training effects for participants with the strongest pre-existing bias (Amir et al., 2011). It makes intuitive sense that re-training of a cognitive bias has the strongest effect in participants who begin the training with a strong cognitive bias. However, the present findings also indicate that matching on the individual level will be difficult. Our hypothesis that weak EC would predict a stronger effect of alcohol-avoidance training was not confirmed. We did find that age moderated the treatment effect, and higher age is correlated with weaker EC, as measured with the Stroop task, and with a stronger short-term training effect. Indeed, an earlier study of CBM found moderating effects of the Stroop task in anxiety re-training in a non-clinical sample (Salemink and Wiers, 2012). In the present study, this moderating effect may have been hidden because the Stroop scores correlated with age and long-term alcoholism, which is also likely to affect EC abilities negatively (Fernandez-Serrano et al., 2011). In the current study, age was correlated with a number of other variables (see Table 5), for instance, older patients reported a longer history of alcohol problems, but lower AUDIT scores (less severity). Note that there are also indications that the number of previous detoxifications is related to brain damage (Crews and Boettiger, 2009; Duka et al., 2011), although here no correlation was found with the Stroop task as a measure of EC. Concerning social variables, being older was associated with a higher chance to be employed and a higher satisfaction with employment (maybe indicating lower social stress levels). Even though none of these variables by itself predicted the effectiveness of CBM, it may be the combination of lower social stress and a comparably mild form of alcohol dependence that maximizes the effect of CBM. In sum, CBM may support older patients by improving their inhibitory control, or by triggering the need for control in the presence of alcohol cues (cf. Gladwin et al., 2011). In turn, this could lead to less relapse when combined with rather low stress levels and low addiction severity.

From a broader developmental perspective, the present findings are interesting as well. They clearly reject the notion that CBM can only have an influence on young malleable brains. Somewhat surprisingly, we found more positive effects for older alcoholic patients. These findings are promising from a treatment perspective. While many individuals (especially men), at some point in their life experience problems with alcohol, many spontaneously "mature out" of these problems (Sher et al., 2005; Littlefield et al., 2009), and also in adult community samples many individuals succeed in spontaneous recovery without formal treatment (Sobell et al., 2000). People who enter formal treatment are typically older and have comorbid other psychiatric problems (e.g., depression, often caused by alcoholism). In addition to working on motivation for abstinence (a typical element in treatment), CBM may train control over the impulse to drink again in a concentrated way, and the alcohol-stimuli may help to trigger this ability in risky situations after treatment discharge (Gladwin et al., 2011). In addition to CBM approaches, one could also investigate training of general EC abilities, with first promising findings in healthy older adults (Buitenweg et al., 2012; Li et al., 2008), in stimulant abusers (Bickel et al., 2011) and in problem drinkers (Houben et al., 2011a,b). Goal-management and mindfulness training have provided initial promising results in addiction (Alfonso et al., 2011), also interventions with a cognitive training element. Clearly, more research is needed on these exciting new possibilities to supplement traditional treatment for addiction with varieties of training-interventions.

Finally, even though these results are promising, there are some noteworthy limitations of the current study. First, the measure of EC used here was a variety of the classical Stroop task, which may have been easier than the original Stroop task. Replicating the present study with a more demanding version of the Stroop task and with other tests of executive functions would seem an important next step. For instance, working memory may be a promising candidate because it has also been found to moderate relations between implicit processes and addictive behaviors (Grenard et al., 2008; Thush et al., 2008). Second, brain activity during the task could also be measured (cf., Brewer et al., 2008). Third, both the current study and the one by Wiers et al. (2011) were conducted in the same clinic and were carried out by the same research group. To draw firm conclusions about the general use of this CBM as a treatment add-on in addiction, it needs to be tested in a multi-center study with different treatment facilities. This would show whether the beneficial effects of alcohol-avoidance training are independent of the combination with certain types of treatment. Further, success of the CBM treatment add-on may depend to some extent on the motivation of the patients. Even though Wiers et al. (2011) showed that a sham-training did not lead to significant outcome improvement, some level of motivation to closely follow instructions may be important for success (for a related discussion on adding CBM to existing treatments for anxiety, see Beard et al., 2011). Future research should try to optimize the link between motivating "treatment as usual" and CBM, but we acknowledge that this may be difficult in a typical randomized controlled study design, and may require different designs (e.g., Teachman et al., 2008).

One important line of future research is to identify necessary conditions for the CBM to be effective. So far we know very little about the optimal number of training sessions, the spacing of training sessions, the length and intensity of training sessions, or the predictors that will make a positive effect of CBM more likely. One would assume that more training sessions would enhance the effects of CBM on abstinence rates. However, comparing the study by Wiers et al. (2011, 4 training sessions) to this study (12 training sessions), it becomes obvious that more training sessions do not lead to higher abstinence rates. It is clear, though, that more than one session is necessary: Single-session CBM has not yielded generalized success in addictions (Field et al., 2007; Schoenmakers et al., 2007), while all studies with positive results (including the present one) have used multiple sessions (Fadardi and Cox, 2009; Schoenmakers et al., 2010; Wiers et al., 2011). Therefore, the optimal amount of training sessions is a question that needs to be addressed. A related domain of further applied interest concerns the possibility of a "take-home" training: Since CBM is simple and computerized, patients could start their training in the clinic and then continue it at home, which might increase the transfer and success achieved with the training.

Another issue concerns mediation and moderation. The present finding that age moderated the effectiveness of the A-AAT retraining is valuable when it comes to matching trainings to patients. However, the fact that age correlated with a number of other potential predictors makes it important to disentangle these variables in future studies: What exactly is it that makes older patients benefit more from alcohol-avoidance training than younger patients? Nevertheless, this is a promising finding, given that many patients are older and have been addicted for a long time, it can be tentatively concluded that training may actually help these individuals. Further, neurocognitive research (using EEG or fMRI) may be needed to improve our understanding of the mediating mechanisms of successful training (for initial findings in the domain of anxiety, see Browning et al., 2010; Eldar and Bar-Haim, 2010). In addition, a direct comparison of general EC training (Bickel et al., 2011; Houben et al., 2011a,b) with CBM-training (which always includes disorder-specific stimuli) is needed. This could answer questions like: to what extent is it better to cue control by disorder-relevant stimuli and are similar brain mechanisms affected by these different types of training?

5. Conclusion

In conclusion, CBM seems to be a promising treatment add-on for the treatment of addiction as well as other psychopathology (for a review and meta-analysis, see Bar-Haim, 2010; Hallion and Ruscio, 2011). Older people appeared to profit most from the training, but we acknowledge that this variable is correlated with a number of other variables. Nevertheless, this is an important finding, given that alcoholism is a progressive neurocognitive developmental disorder, with many young people spontaneously maturing out, and many older people in treatment facilities, who need help to overcome their addiction. The next research steps should be to clarify underlying mechanisms in CBM in comparison with other training-interventions, and to address issues of implementation (e.g., number of training sessions, spacing of training sessions, connection with treatment as usual). Finally, for both theoretical and clinical reasons, it seems important to further address the question of moderation: Which training works best for whom?

Conflicts of interest

We declare that there are no conflicts of interest. None of the data has been previously reported.

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