Training alcohol-related attentional biases in alcohol-dependence. What are the neurocognitive effects?

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The aim of the proposed study is to examine the effectiveness of this new form of attentional bias training as an add-on to treatment-as-usual in facilitating abstinence from alcohol use in patients diagnosed with alcohol dependence. Additionally,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44641

Source
ToetsingOnline

Brief title
ABM training fMRI

Condition

- Other condition

Synonym
alcohol addiction and alcohol dependence

Health condition

alcohol dependence

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO (VICI),Charity: ERAB: The European Foundation for Alcohol Research

Intervention

Keyword: Alcohol dependence, Attentional training, fMRI, MRS

Outcome measures

Primary outcome

The primary outcome measure will be the number of alcohol-containing drinks a patient drank during the training period and during the month after the end of the training. This will be assessed using a questionnaire-based self-report measure.

Secondary outcome

We will use two cognitive tasks in the MRI scanner and collect BOLD response data in the presence of stimuli associated with alcohol, relative to stimuli not-associated with alcohol in both tasks:

In the Concurrent Flanker/Alcohol-attentional bias task (CFAAT; Nikolaou et al., 2012; 2013), the Eriksen Flanker task is superimposed on backgrounds of alcohol-related or neutral pictures. Participants respond to the direction of a central *target* arrow and ignore adjacent congruent or incongruent flanking-arrows, in the presence of task-unrelated neutral or alcohol-associated pictures. 20 alcohol-related and 20 neutral grey-scaled pictures will be used. Each picture will be presented with each possible flanker arrow presentation (i.e. arrows congruent pointing left; incongruent

pointing left; congruent pointing right; incongruent pointing right). 80 filler trials, in which the task is performed in the absence of the background pictures, will also be included in order to reduce habituation with the background pictures. Images will be presented in a pseudorandom order so that the same flanker condition and the same background condition will not be presented on more than three consecutive trials. Each trial begins with the presentation of a central fixation cross of varied duration (850-1150ms). The fixation cross is replaced by the stimulus-display which is presented for 500ms, and consists of the centrally-presented row of *target* and *flanking* arrows superimposed on the task-unrelated background displays. Each trial terminates when the response interval ends. Total task duration is 9 minutes. This task measures attentional biases to alcohol-related stimuli under conditions in which cognitive/attentional load is manipulated.

The Alcohol-related cue reactivity task is an event related task that involves the presentation of 30 alcohol-related, 30 neutral and 10 target grey-scaled images one at a time. Participants will be told to pay careful attention to the images. They will be asked to respond via button press every time a target picture (a picture of an animal) appears, as quickly and as accurately as they can. Alcohol-related images will be photos of alcohol bottles and glasses and individuals drinking alcohol. Control images will be visually matched to the alcohol-related images in content, composition, complexity and luminosity but they will depict non-alcoholic beverages and people drinking non-alcoholic

beverages. Each trial will begin with the presentation of a fixation cross for a jittered duration between 2 and 6 seconds. The fixation cross will be replaced by one of the photos from one of the conditions, which will be presented for 4 seconds. The blank screen response interval will last for 1250 msecs. Total task duration will be 11 minutes.

To verify the validity of the alcohol-related cues in inducing craving, relative to the control and target images, participants will perform an image-rating task outside the MRI scanner, after scanning. All images will be presented for a second time on a computer screen, followed by the question *How much do you crave an alcoholic drink?*. Participants will be asked to respond to the question on a visual analogue scale ranging from -50 (not at all) to 50 (extremely).

Study description

Background summary

Recent estimates within the EU, place the yearly economic burden from alcohol abuse and dependence at 155 billion euros. Despite these enormous costs, less than 10% of individuals diagnosed with alcohol dependence receive formal treatment, and of those, only 28% achieve abstinence, suggesting that further research in treatment-development is warranted (Rehm et al., 2012). Ideally, treatment evaluation should be multifactorial, and include indices able to assess the neurocognitive effects of an intervention (e.g. neuroimaging during performance of cognitive tasks), in addition to typical measures of treatment-outcome (i.e. degree of alcohol craving, and relapse propensity). Such designs would allow the assessment of whether changes in real-life drinking behaviours are mediated by treatment-induced ameliorations of neural and cognitive processes known to be impaired in alcohol use disorders (Marhe et al., 2014).
Alcohol use disorders are characterised by augmented attributions of

motivational salience to alcohol itself and to stimuli that predict alcohol availability, and by deficits in frontal brain regions implicated in *top-down* cognitive control processes (e.g. Goldstein & Volkow, 2011). Augmented attributions of salience are reflected in stimulus-driven, or *bottom-up*, neural, behavioural, and cognitive responses to alcohol-predicting cues, while deficits in cognitive control processes are reflected in, for example, the inability to regulate these stimulus-driven responses. *Biased* responses to alcohol-associated cues develop over the course of alcohol abuse. For example, both non-dependent heavy alcohol-drinkers and alcohol-dependent patients show *attentional biases* to environmental stimuli associated with alcohol (i.e. they preferentially allocate their attention to, and are distracted by alcohol-associated cues; Cox et al., 2000). Biases are thought to contribute to the development of binge-drinking behaviours, and the maintenance of alcohol addiction, and have been related to alcohol craving, and the propensity to relapse following periods of abstinence (Wiers et al., 2013).

Consequently, recent research has focused on developing interventions aimed at moderating drinking behaviour, and facilitating abstinence, by reducing these alcohol-associated biases. *Attentional bias modification* (ABM), is an attentional re-training technique developed, and originally applied clinically, for the amelioration of symptoms of anxiety (e.g. Amir et al., 2009). Applied to heavy-drinkers, a single session of ABM training reduced alcohol-associated attentional biases (Schoenmakers et al., 2007; Field et al., 2005), but the effect did not generalize to untrained stimuli. Multiple sessions of ABM in problem drinkers (Fadardi & Cox, 2009) reduced heavy drinking, and decreased attentional biases to untrained stimuli, but there was no control group. Our lab conducted the first small Randomized Controlled Trial of ABM in detoxified treatment-seeking alcohol-dependent in-patients. The training was successful in (a) reducing attentional biases to alcohol-related stimuli; (b) increasing the time-to-relapse; and (c) reducing the time before in-patients were released from treatment centres (Schoenmakers et al., 2010). Thus, initial data suggest that reducing attentional biases using ABM, results in clinically-relevant changes in alcohol-associated behaviours.

However, the data have not always been consistent, and findings suggest that behavioural change through ABM is possible only in the cases where attentional biases are successfully reduced (Clarke et al., 2014). ABM in alcohol research has typically been implemented using adapted versions of the visual-probe paradigm. Participants see pairs of alcohol-related and neutral images (usually pictures of soft-drinks), and are asked to respond via key-press to the direction of a subsequently presented probe (e.g., an arrow pointing up or down). Attentional allocation is trained away from the alcohol-associated images, because on each trial of training the probe replaces the neutral image. Recently, researchers in the area of anxiety developed a novel ABM method based on the visual search paradigm. Participants are trained to search for an image depicting positive emotion within arrays of images depicting negative emotions. Preliminary data from our lab suggests that visual search ABM training, relative to control training, is effective in reducing both attentional biases to anxiety-provoking images, and self-reported feelings of social phobia in

anxious adolescents, with stronger effects than the more standard dot-probe ABM (De Voogd et al., 2014).
We recently adapted De Voogd and colleagues* (De Voogd et al., 2014) visual search ABM, and ran an online pilot study on its effects on heavy-drinking university students* alcohol-associated attentional biases and weekly alcohol use. The *alcohol-visual-search-training* (AVST) requires searching for the image of a non-alcohol-containing drink in arrays of images depicting alcohol-containing drinks. The control training requires searching for a 5-petal flower in arrays of 7-petal flowers (as in De Voogd et al. 2014). The group that received the AVST training, relative to the group that received the control training, showed a significant reduction in the amount of time it took to select the image of the non-alcohol-containing drink from arrays with distracting alcohol-associated images, suggesting a significant improvement in the ability to ignore alcohol-associated distracters in this group. In addition, the same group showed significant reductions in attentional biases as measured using the dot probe task, suggesting that AVST training generalized to influence performance on other tasks of attentional biases. With respect to the amount of units participants consumed in the week before and the week after the training, we found a trend for reduced drinking in the AVST-training group that approached significance (0.075). In addition, when we examined drinking during training, the AVST group showed a significant reduction in drinking units relative to the control group.
An attractive aspect of the AVST is that it may produce its effects by strengthening *top-down* cognitive control processes in the presence of alcohol-associated stimuli. Neurocognitive research suggests that stimuli which are not task/goal-relevant, but possess strong motivational salience, can interfere with selective attention to less salient yet task-relevant stimuli (Krebs et al., 2010). A possible mechanism underlying this effect is that the *top-down* cognitive control processes, necessary for resolving distracter interference by enhancing the attentional processing of the task-relevant information (Botvinick et al., 2001), are weakened, when the task/goal-irrelevant distracters represent motivationally-salient stimuli. Indeed, a recent functional imaging study (fMRI) demonstrated that the interfering effect of task-unrelated alcohol-associated stimuli in heavy drinkers, was coupled with reduced neural responses in areas of the prefrontal cortex that were also activated by the need for cognitive control in the absence of alcohol-associated cues (Nikolaou et al., 2013). AVST training consistently renders alcohol-associated stimuli as task/goal-irrelevant distracters, and non-alcohol-associated stimuli as task-related targets. Additionally, by contrast to most dot-probe training paradigms visual search training does not only involve learning to allocate attention to the non-drug-associated cue, but it also requires learning to resolve the attentional interference that is produced by the alcohol-associated distracters. Thus, AVST should train the recruitment of *top-down* cognitive control in the presence of alcohol-associated stimuli. At the same time however, the control training trains cognitive control more generally. Thus, given that cognitive control processes are thought to be deficient in alcohol

dependent patients, both the control and the real training conditions should ameliorate deficits associated with cognitive control, but the real training condition does this in the presence of alcohol-associated stimuli when the deficient control resources are weakened by the presence of these stimuli. This reasoning is corroborated by our findings in students, whereby both training conditions resulted in reductions in drinking post-, relative to pre-training, however the biggest effect was seen in the real training group.

Study objective

The aim of the proposed study is to examine the effectiveness of this new form of attentional bias training as an add-on to treatment-as-usual in facilitating abstinence from alcohol use in patients diagnosed with alcohol dependence.

Additionally, the study aims to explore the neurocognitive mechanisms by which this new form of ABM training has its effects, by collecting fMRI data both before the start of the training and after the training has been completed.

Study design

Design
Each patient will be randomly assigned to one of two ABM training groups: a control group and an experimental group (see "intervention" section for details). Allocation will be random, double blind and stratified by gender and will be conducted by a computer.

Testing
Each participant will take part in 2 testing sessions, and a second session in the week after the participant has completed his/her allocated training regimen. Both, will take place at the Spinoza Centre in Amsterdam. In between these two sessions, they will complete 6 x 20 minute training sessions online. A month after the end of the scanning session, participants will complete a final follow-up assessment.

Baseline Session
During the baseline session, informed consent will be taken and participants will have the opportunity to experience the scanning environment by undergoing a dummy scan. Once participants have declared that they would feel comfortable in the scanner, and that they are happy to continue, we will administer the following measures:
(1) Medical history questions
(2) The Beck Depression Inventory (BDI; Beck, 1961)
(3) The Barratt Impulsiveness Scale
(4) Zelf-beoordelings Vragenlijst (Van der Ploeg et al., 1980)
(5) Drug-use history using CORE full
(6) Drug-use previous month using CORE short

(7) Time-Line Follow back (full)
(8) The Fagerstrom Test for Nicotine Dependence (FTND; Fagerstrom, 1978)
(9) The Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993)
(10) Drinking Motives Questionnaire-Revised (DMQ-R; Cooper, 1994)
(11) Obsessive-Compulsive Drinking Scale (OCDS; Anton et al., 1995).
(12) Penn Alcohol Craving Scale (PACS, Flannery et al., 1999).
(13) Alcohol-use history (Age of onset of regular alcohol consumption; the age of onset of problem drinking; the number of previous attempts at abstinence with details of whether they were assisted attempts and conducted in inpatient or outpatient settings; and the number of days/weeks since the last use).
(14) The Alcohol Dot Probe task (e.g. Schoenmakers et al., 2008)
(15) The Alcohol Visual search assessment task (e.g. Kruijt et al., 2013)
These will be followed by the completion of a backward digit span pen-and-paper task, and a practice run of the Concurrent Flanker Alcohol Attentional bias task (CFAAT; Nikolaou et al., 2013a; 2013b).
Then, patients will be placed in the MRI scanner and undergo the scanning procedure (see below), which will include the following tasks:

Baseline assessment inside the scanner
(1) Baseline cue reactivity
(2) Baseline run of the Concurrent Flanker Alcohol Attentional bias task
Upon completion of scanning, participants will rate their craving to the images presented in the cue reactivity task. At the end of the entire baseline session, participants will be given an information booklet providing information regarding the online training procedure. This booklet will inform them which site they should visit, how often they should visit it, and what they should do when they are on the site. Before they leave, patients will be reimbursed for their travel. The baseline session should not last longer than 135 minutes.

Post-training scanning session (1 week after completion of training regimen)
The scanning session will begin with a practice run of the Concurrent Flanker Alcohol Attentional bias task (CFAAT; Nikolaou et al., 2012; 2013), which will be used in the scanner. This will be followed by the completion of: (1) Time-Line Follow back (Sobell & Sobell, 1995), and (2) the Penn Alcohol Craving Scale (PACS, Flannery et al., 1999) to assess drinking and craving post-training. We will then assess alcohol-associated attentional biases for the final time using the dot probe task and the visual search assessment task. This will be followed by the scanning procedure, minus the structural scan (see below).

Scanning procedure (both sessions: baseline and post-training session, though no structural scan will be taken at the post-training session
The MRI protocol in the 3T Phillips MRI scanner will be as follows:
(a) A structural scan (10 minutes)
(b) EPI fMRI sequence during performance of the CFAAT (9 minutes)
(c) EPI fMRI sequence during an alcohol cue reactivity task (11minutes)

The fMRI sequences will be presented in the same order for each participant.

Upon completion of scanning, participants will rate their craving to the images presented in the cue reactivity task. Thus the session will not take longer than one hour and 60 minutes. At the end of the session, patients will be reimbursed for their travel.

Final follow-up session
The follow-up session will take place one month after the Scanning session, and will involve completing the Time-Line Follow-Back Questionnaire and the Penn Alcohol Craving Scale online, to assess whether the intervention affected real-life drinking behaviours and subjective reports of craving. Upon completion of the final questionnaire assessment, participants will be sent a Debriefing Brochure. At this time, they will also be sent a cadeaucheque worth ¤40, as reimbursement for their participation.

Intervention

ABM Training
Each participant will be randomly assigned to one of two ABM training groups based on the work by Kruijt et al (2013):
(1) Control-training group (Participants will be trained on an alcohol-unrelated visual search task: Participants will be shown a 4x4 grid of 16 pictures, 15 of which will be images of 7-petal flowers and 1 will be an image of a 5-petal flower. During the training, the participants will be asked to search for the picture with the 5-petal flower and ignore the other pictures. Thus visual selective attention will also be trained in this condition)
(2) ABM-training group (Participants will be trained on an alcohol-related visual search task: Participants will be shown a 4x4 grid of 16 pictures, 15 of which will be images of drinks containing alcohol and 1 will be an image of a drink that does not contain alcohol. Training will focus on asking patients to locate the non-alcoholic drink. Thus visual selective attention will be trained to specifically and consistently ignore alcohol-associated images)

There will be 6 training sessions in total, each lasting for 20-minutes. All training sessions will be conducted online

All training sessions will be completed by each patient on their own at home. Patients will be provided with information explaining which website they should visit and how they should log on to the website, in the baseline session. They will also be told that they will receive emails notifying them when they should do a training session, and reminders emails if they have forgotten to complete a sessio. Patients will also be aware that the main researchers will be able to monitor that they have indeed completed each training session.

Neither the main experimenter nor the participants will be aware of the

assigned training, as the allocation will be conducted randomly by the computer as soon as each patient logs on to the website. Patients will be aware that the main experimenter is not aware of the type of ABM that they are given.

Study burden and risks

(a) Patients will be required to complete 6 x 20-minute online training sessions. Due to the fact that the training sessions are conducted online, patients are able to complete them at their own time and on their own computer. In addition, the training will not impact in any way on the treatment that patients will already be receiving as it will be unrelated. We therefore do not foresee any risks associated with doing the training. On the contrary, based on previous findings it is expected that this additional form of treatment will have beneficial effects on real-life drinking behaviours for the patients as we expect it to facilitate the maintenance of abstinence for a longer period of time.

(b) We do not foresee any risks associated with completing the tasks or undergoing scanning. The tasks are cognitive tasks that should not produce any distress on the part of the patients. In addition, the patients will be monitored closely and will be given the opportunity to stop the tasks and the scanning if they so wish at any point in the experimental session. The scanning session and the baseline session will however be time consuming as they will require travelling to the appropriate centre , and spending at least an hour and 30 minutes for each session to be completed. We will however include several pauses throughout both sessions and participants will be reimbursed for both the entire study and for their travel to and from the testing centres.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Male and female alcohol dependent out-patients, aged between 18-70 years
* Current DSM-V diagnosis of alcohol dependence
* Right-handed.
* Within the normal BMI range (18-30).
* Able to speak and understand Dutch.
* Able to speak and understand English.

Exclusion criteria

* Impairments in visual processing or in hand-eye coordination (this would make it difficult for patients to perform properly in the scanner)
* Being on anticraving medication (naltrexon, campral of baclofen).
* No previous or current abuse of drugs other than alcohol (excluding nicotine, cannabis and caffeine)
* Pregnancy, trying to conceive or breastfeeding.
* Having any metal implants, working or having worked with metal, teeth braces or bridges, tattoos above the shoulder, or cardiac pacemaker.

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-05-2016
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	29-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL49033.018.14