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It's Debatable

What's in a Trial? On the Importance of Distinguishing between Experimental Lab-Studies and Randomized Controlled Trials; the Case of Cognitive Bias Modification and Alcohol Use Disorders

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Abstract

Objective: Recently, the National Institutes of Health (NIH) redefined clinical trials to include any study involving behavioral or biomedical interventions. In line with a general framework from experimental medicine, we argue that it is crucial to distinguish between experimental lab-studies aimed at revealing a mechanism underlying behavior, and Randomized Controlled Trials (RCTs) in clinical samples aimed at testing efficacy of an intervention. **Methods:** As illustration, we review the current state of the evidence on the efficacy of Cognitive Bias Modification (CBM) interventions in alcohol use disorders. **Results:** A recent meta-analysis (Cristea et al., 2016; PloSOne; 11(9), e0162226) "cast serious doubts on the clinical utility of CBM interventions for addiction". Their analysis combined experimental lab-study and RCTs. We demonstrate that when studies are differentiated regarding study-type (experimental lab-study or RCT), mode of delivery (controlled experiment or internet) and population (healthy volunteers or patients), the following effects are found: (1) short-lived effects of CBM on drinking behavior are found in experimental lab-studies in students, but only if the bias is successfully manipulated; (2) small but robust effects of CBM when administered as an adjunct to established treatments in clinical settings in RCTs with alcohol-dependent patients, and (3) non-specific effects (reduced drinking irrespective of condition) in RCTs of CBM administered online to problem drinkers. **Conclusions:** We discuss how CBM might be improved when it is better integrated into regular treatment, especially cognitive behavior therapy, and conclude that disregarding the difference between experimental lab-studies and RCTs can lead to invalid conclusions.

Introduction

Recently, the US National Institutes of Health (NIH) broadened the definition of clinical trials to include all interventions with health-related biomedical or behavioral outcomes, including minimal manipulations such as asking participants to monitor their food intake, which has led to an uproar among brain and behavioral scientists (Reardon, 2017). In line with a general Experimental Medicine (EM) framework (Sheeran et al., 2017), we argue that it is crucial to distinguish between experimental lab-studies aimed at exploring and testing mechanisms underlying human behavior (typically in healthy volunteers), and randomized controlled trials (RCTs) aimed at testing efficacy of an intervention in a clinical sample. This distinction is important both when designing and synthesizing research. As an illustration, we discuss the state of affairs concerning the effects of Cognitive Bias Modification (CBM) in addiction. CBM refers to a class of behavioral interventions which aim to directly interfere with automatically activated cognitive processes, hypothesized to play a role in maintaining psychological disorders (Wiers et al., 2013). A recent meta-analysis "cast serious doubts on the clinical utility of CBM interventions for addiction problems" (Cristea et al., 2016). We argue that this conclusion is invalid because the analysis combined qualitatively different types of studies, representing different phases of the EM framework: experimental lab-studies in students not motivated to change and RCTs with patients motivated to change. In order to highlight differences between types of studies, we start with a brief history of CBM in anxiety, where it was first invented and applied to clinical groups, and include lessons learned from this literature. We then outline the crucial difference between experimental studies and clinical trials using a general EM-framework. Using this distinction, we review the literature on CBM in relation to Alcohol Use Disorder (AUD). We end with ways forward for CBM in addiction and general conclusions about the importance of distinguishing experimental lab-studies and RCTs.

CBM in Anxiety: Lessons Learned

CBM started with the seminal study of MacLeod and colleagues (2002), who randomly assigned student volunteers to a condition in which their attention was trained toward or away from threatening stimuli. The latter group showed less anxiety during a subsequent stressful task compared to the first group. Note that this study concerns a psychological experiment and not a clinical trial; the goal was to test the hypothesized causal role of the targeted process in relation to anxiety-symptoms; earlier studies had reported correlations between attentional bias (AtB) and anxiety, but experimental manipulation is required to establish causality (Spencer et al., 2005). Note further that in experiments, psychological constructs can be manipulated in both directions: toward or away from disorder-relevant stimuli, which is typically not done in clinical trials.

After promising findings in these first lab-experiments, RCTs were conducted in clinical samples with anxiety disorders, with remarkable successes (i.e., reduced attentional bias and reduced anxiety, e.g., Amir et al., 2009). Given these initial successes and the fact that CBM typically employs computerized interventions, large online RCTs were conducted. These largely resulted in non-significant findings, related to the fact that in most cases the targeted bias was not changed when CBM was delivered online (Macleod and Clarke, 2015). A meta-analysis on CBM in anxiety and depression (Cristea et al., 2015) concluded that CBM may have small effects on mental health problems, but it is also very possible that there are no significant clinically relevant effects. However, a re-analysis of the same data confirmed that CBM has the hypothesized emotional or behavioral effects when the cognitive bias is successfully changed, but does not if the bias is not changed (Grafton et al., 2017; MacLeod and Grafton, 2016). Moreover, other meta-analyses focusing on clinical samples (Heeren et al., 2015; Linetzky et al., 2015) concluded that there are reliable effects of CBM on bias and clinical symptoms. A recent pooled patient-level meta-analysis (including

original data from 13 clinical studies), confirmed this (Price et al., 2016), with training setting (clinical context or online) as a significant moderator (smaller effects for training online). Hence, from CBM in anxiety, we derive first, the importance of distinguishing between experimental lab-studies and RCTs; second, that within RCTs, it is important to distinguish between settings (online or clinical); and third, that in order to establish effects on clinically relevant outcomes, it is crucial to test whether the targeted bias was successfully manipulated.

CBM in Addiction: What's in a Trial?

In the field of addiction, a similar development can be observed. CBM in addiction has its origins in cross-sectional and prospective studies which demonstrated that individual differences in cognitive biases are associated with individual differences in substance use (Field and Cox, 2008; Rooke et al., 2008). First experimental studies tested the causal status of the biases, by testing whether changing a cognitive bias in students resulted in short-lived changes in alcohol intake directly after the manipulation (Field et al., 2007; Field and Eastwood, 2005; Schoenmakers et al., 2007; Wiers et al., 2010). Again, note that in some of these studies one experimental group was trained toward alcohol to test whether this resulted in increased drinking in a bogus 'taste test', compared with a group that was trained away from the alcohol stimuli, something not done in RCTs. Results indicated that cognitive biases for alcohol could indeed be changed (detailed below).

Next, RCTs were conducted, in which alcohol-dependent patients received multiple sessions of CBM or placebo-training in addition to psychosocial therapy (typically Cognitive Behavior Therapy, CBT). Results were promising, for AtB-training in a first small RCT (Schoenmakers et al., 2010), and consistent positive outcomes (detailed below) were found for Approach-bias (ApB) retraining (Eberl et al., 2013; Manning et al, 2016; Wiers et al., 2011). In the third category (online training), the only published study reported a main effect

of time, indicating that problem drinkers successfully reduced their drinking in all conditions, including a sham-training condition (R. W. Wiers et al., 2015).

Cristea and colleagues (2016) conducted a literature search to identify RCTs that compared CBM for addiction with either a control treatment or another active treatment. Similar to the recent NIH policy, they stated, "no filters were used as to not miss any studies that might not have presented themselves as RCTs, but as experimental studies" (p3). We have questioned the validity of this classification because of the qualitative difference between experimental lab-studies and RCTs in brief commentaries (Field et al., 2016; Wiers, 2016). We now elaborate this general point using a general framework from EM (Sheeran et al., 2017).

Experimental Lab-Studies and Clinical RCTs represent different phases of EM

Recently, a general EM-framework was applied to the development of behavior change interventions (Sheeran et al., 2017). It identified four distinct steps: (1) identification of a potentially modifiable psychological process associated with the problem behavior, (2) experimental manipulation of the target psychological process in order to investigate its causal influence on the problem behavior, (3) development and evaluation of novel interventions that lead to robust changes in the target psychological process, (4) RCTs that investigate whether an intervention developed in the third stage leads to robust behavior change, and if this behavior change is mediated by changes in the psychological process.

Psychological experiments that experimentally manipulate cognitive biases in order to investigate their causal influence on substance use outcomes correspond to the second step (and, to a lesser extent, the third step) in this EM-framework. They are an important precursor to the fourth step (RCTs), but psychological experiments and RCTs should not be confused, for a number of reasons. First, laboratory experiments often administer a brief 'dose' of CBM and investigate the short-term effects on substance use or associated

outcomes (e.g., subjective craving or the amount of alcohol consumed in a bogus taste test) immediately after the manipulation. Second, participants who take part in CBM experiments are usually not informed that an experimental manipulation they might receive intends to change their substance use and often report no awareness of the manipulation after a single session of CBM (e.g., Schoenmakers et al., 2007; Wiers et al., 2010; Houben et al., 2011). In contrast, participants in RCTs are explicitly informed that they may receive an intervention.

Third, in psychology experiments, participants (often students) participate for financial incentives or course credits. Motivation to change substance use is not a criterion for inclusion in these studies, and usually not assessed. Students also typically do not show substantial substance-related problems or symptoms of dependence, which are the essential features of the target population for clinical applications of CBM. In contrast, volunteers in RCTs of CBM a) do experience clinically relevant substance-related problems and/or are clinically diagnosed with AUD, and b) are motivated to change their behavior, and in many cases, receive CBM in addition to treatment, which typically incorporates a motivational component. The clear demarcation of the target population of a treatment intervention is one of the key elements in designing a systematic review, since it affects the relevance of the meta-analysis for the disease of interest (chapter 5 of the Cochrane handbook for systematic reviews of interventions, the gold standard guidelines for RCT meta-analyses; O'Connor et al., 2008). The inclusion of experimental lab-studies with non-clinical volunteers (phase 2) would bias the applicability and generalizability of the results of CBM as a *clinical intervention* (phase 4 of EM).

--- Table 1 ---

As summarized in Table 1, when comparing experimental studies and RCTs, participants differ on at least two main parameters defining the scope of the study: patients are aware that they receive an intervention and are motivated to change their behavior, while

for healthy student-volunteers both are typically not the case. Based on the CBM-anxiety literature, we further distinguish between two subtypes of RCTs, those in a clinical setting, and online studies in which self-identified problem drinkers receive CBM as a stand-alone intervention. These also differ in many respects: the presence or absence of other treatment, the clinical context, possibly the effectiveness of the CBM intervention (lack of experimental control in online studies could lead to less efficient bias-change). Further, the treatment goal is different: abstinence in in-person RCTs, while in online interventions participants choose their own goal, typically reduced drinking (R. W. Wiers et al., 2015).

Cristea and colleagues (2016) reported a small positive effect of CBM on substance use outcomes, but reported that the effect size was related to risk of bias, for which they used five criteria from the Cochrane Collaboration's risk of bias assessment tool (Higgins et al., 2011): (a) adequate generation of allocation sequence, (b) concealment of allocation to conditions, (c) prevention of knowledge of the allocated intervention to assessors of outcome, (d) prevention of knowledge of the allocated intervention to participants and personnel, (e) dealing with incomplete data. As noted, the Cochrane tool is the gold standard for assessment of risk of bias in RCTs (for which it is intended) – but it must be interpreted with caution when applied to lab-experiments. Cristea et al. (2016) did not do this. For example, the majority of laboratory studies were rated as 'unclear' risk of bias because they did not report the method by which participants were randomized to conditions. However, this score should have been 'low', because in CBM randomization is typically done by the computer program. The fact that these details were missing from many papers reflects the different reporting standards for experimental lab-studies and RCTs (see CONSORT guidelines, Boutron et al., 2017). Further, studies were rated as unclear or at high risk of performance bias if participants' awareness of the training contingencies was not measured after CBM, or if awareness was measured and more than 50% of participants were aware of the contingencies.

This is misjudged, because coding of the risk of performance bias is problematic, and often not possible, for non-pharmacological interventions such as psychological interventions or surgery (Boutron et al., 2008; Schulz and Grimes, 2002). Hence, we fundamentally disagree that if participants develop awareness of the contingencies that are applied during CBM this indicates increased risk of bias in the study. It is even possible that participants must develop awareness of contingencies for CBM to have effects (Field et al., 2007).

Review of the different types of CBM studies in the alcohol domain

Given the reasons outlined above to distinguish between experimental lab-studies and RCTs and the fact that there are only a few true RCTs, we present a narrative review of the current state of affairs. In doing so, we only focus on alcohol, for two reasons. First, the number of CBM studies is larger for alcohol than for smoking; second, the CBM-smoking literature has recently been reviewed elsewhere (Mühlig et al., 2017). We included all alcohol-related studies included in Cristea et al. (2016), and added studies that were overlooked (e.g., Houben et al., 2012, a replication of Houben et al., 2011; and studies on evaluative conditioning), or that came out later. In line with MacLeod and Grafton (2015), we indicate for each study whether the targeted bias was successfully changed and whether effects on behavior were found. In line with the EM-framework, we distinguish between experimental lab-studies with student volunteers, in which effects on alcohol intake in the lab are typically assessed directly after the manipulation, and RCTs, in which duration of abstinence is the typical outcome measure. Unlike Cristea et al., we did not consider subjective craving as an outcome measure, because it is virtually absent in an inpatient "dry" clinical setting (e.g., Wiers et al., 2011), and difficult to compare with student volunteers who do not realize they receive an intervention, and in some cases participate in a bogus taste-test.

Experimental Studies Manipulating Cognitive Biases in Student Volunteers

Table 2 summarizes the results. Five studies targeted AtB, five ApB and nine memory biases for alcohol. In the latter category, we included studies in which inhibition to alcohol cues was trained, but not studies that trained general inhibition or working memory. The reason is that specific inhibition to one category of stimuli changes memory associations for that category (Houben et al., 2011, 2012), but does not affect general inhibition (Houben et al., 2012). Training of general executive functions is conceptually different: no specific cognitive bias is targeted but the general cognitive ability to resolve interference and overcome biased information processing (Wiers et al., 2013). This type of training also requires many more sessions (see Houben, Wiers, et al., 2011; Wiers et al., 2013).

All student-studies manipulating alcohol-AtB used varieties of the visual probe task, based on the original study in anxiety by MacLeod et al. (2002), in which participants' attention was trained away from alcohol in the experimental condition, whereas in the control condition(s) it was not trained (continued assessment, e.g., Schoenmakers et al., 2007), trained toward alcohol (e.g., Field et al., 2005), or both (e.g., Field et al., 2007). In general, no effects were found on untrained stimuli or AtB assessed with another task (Field et al., 2007; Schoenmakers et al., 2007), nor on drinking behavior. One study did report effects on AtB in a different task using eye-tracking (Lee and Lee, 2015), but reported no effect on drinking. Finally, one study reported effects on drinking frequency after repeated training in students (not motivated to change drinking), but did not report changes in AtB (McGeary et al., 2014).

Five studies targeted alcohol-ApB and all used a variety of the alcohol approach avoidance task (Wiers et al., 2009), in which participants push or pull a joystick while responding to a content-irrelevant feature of the stimulus (e.g., pull portrait-pictures, push landscape-pictures). In the experimental condition, participants are trained to push alcohol pictures (which zoom out upon pushing). One study found generalized effects on untrained

stimuli in the same task and to alcohol-approach associations, and an effect on drinking in a bogus taste-test in successfully trained students (Wiers et al., 2010). Lindgren et al. (2015)'s studies used varieties of the original ApB-training to change alcohol-identity associations and found changes neither in alcohol-identity nor in drinking behavior. Another study showed indirect effects of ApB change on alcohol consumption in a post-training bogus taste test in the alcohol-avoid ApB condition (Sharbanee et al., 2014). A recent study tested effects of ApB modification vs. selective inhibition (discussed below) vs. their respective control conditions (Di Lemma and Field, 2017). Both active interventions reduced drinking in a subsequent bogus taste test, but only ApB-training led to the hypothesized change in cognitive bias.

For changing alcohol-related memory associations, four techniques were used. Seven studies used selective inhibition with the Go/NoGo task: in the experimental condition, alcohol pictures are consistently paired with NoGo (stop) cues, while in the control condition there is no such pairing. Two studies by Houben and colleagues (2011, 2012) found a generalized effect on memory associations (assessed with an alcohol-valence IAT) and an effect on reduced drinking in the week after the experiment. Other studies (Boendermaker et al., 2015a; Bowley et al., 2013) found no change in memory-bias nor on drinking. Di Lemma and Field (2017) did find an effect on drinking, but no differential change in reaction times after alcohol pictures. The remaining four studies used different methods. One used an alcohol-variety of the Stop-signal task (Jones and Field, 2013). Two studies used evaluative conditioning (Houben et al., 2010a,b), a procedure in which in the experimental condition, alcohol pictures are consistently paired with negative pictures. One study (Woud et al., 2015) used interpretation-bias training, in which participants in the experimental condition are trained to interpret ambiguous alcohol-related scenarios in a disorder-incongruent way. Effects on drinking were found when the bias was successfully changed (Houben et al.,

2010a,b; Jones & Field, 2013), not when the bias was not successfully changed (Woud et al., 2015).

The overall pattern of results regarding CBM studies in students is mostly consistent with the notion that short-lived effects on behavior are found after successful bias-change and no effects after unsuccessful bias-change (exception: Di Lemma & Field, 2017, for selective inhibition), in line with results in anxiety (MacLeod and Clarke, 2015). This conclusion concurs with another recent meta-analysis summarizing effects of cue-specific response inhibition training in the appetitive domain (Allom et al., 2015): statistically significant, but short-lived reductions in health-compromising appetitive behaviors (alcohol consumption and unhealthy eating) were found. This conclusion is further corroborated in an independent meta-analysis that concluded that the number of successful cue inhibitions was correlated with the effects on eating and drinking (Jones et al., 2016). Overall, the experimental studies in students are important as evidence for step 2 in the EM-framework: they have identified targets for interventions, by demonstrating that a successful manipulation of the cognitive bias results in a short-lived effect on relevant behavior. This indicates that subsequent RCTs are needed to test the (medium- and long-term) clinical efficacy (step 4).

Experimental Studies Manipulating Cognitive Biases in Clinical Trials

Two clinical RCTs used multiple sessions of AtB in AUD patients using training varieties of the visual probe task. The first included 43 AUD patients, who received five sessions of training or sham-training (Schoenmakers et al., 2010), in addition to CBT. AtB for alcohol was reduced in the experimental condition (with generalization to untrained alcohol stimuli). Although there was no robust effect of AtB on the primary outcome measures, there was an indication of clinical impact: patients in the experimental condition were discharged earlier than patients in the control condition and relapsed later. The second study combined 8 sessions of experimental or placebo AtB-training for alcohol and threatening cues in AUD

patients with social anxiety (Clerkin et al., 2016). Alcohol AtB was reduced, as well as AUD outcomes across all conditions, irrespective of training condition (no Time by Condition interaction). Cox and colleagues (2015) combined AtB-training and motivational enhancement.[1] The training paradigm employed was the Alcohol Attention-Control Training Program (AACTP), which had shown promise in an earlier uncontrolled study in which problem drinkers reduced drinking compared to baseline (Fadardi and Cox, 2009). The AACTP uses training varieties of pictorial Stroop-tests and employs increasing levels of difficulty to motivate participants. In Cox et al. (2015)'s study, AACTP and motivational enhancement could both be present or absent (2 x 2 design). AACTP led to reduced drinking in the short term (3 but not 6 months after the intervention). Motivational enhancement reduced drinking 3 and 6 months after the intervention. No interaction effect was found. Effects on AtB were not reported, but the program requires progress in reduction of AtB in order to progress in the program, making it likely that it occurred.

Two large studies tested the effects of alcohol ApB-training as an add-on to CBT (Eberl et al., 2013; Wiers et al., 2011). In the first study (N=214), four sessions of ApB-training resulted in reduced alcohol ApB, with generalization to alcohol-approach implicit associations in the IAT and 13% lower relapse rate a year after treatment discharge, compared with controls (Wiers et al., 2011). In the second study (N=509), the same ApB-training, compared to no training, resulted in 9% lower relapse rate at one-year follow-up, and this effect was mediated by the change in ApB (Eberl et al., 2013). Moderation was also found (stronger effect in patients with strong alcohol ApB before training).

Cristea and colleagues (2016) included one other study of ApB-training in AUD patients, an fMRI study (N=36), aimed at investigating the neurocognitive mechanisms underlying CBM (C. E. Wiers, et al., 2015). It was found that CBM reduced cue-induced

[1] Participants included students, but they were recruited to learn skills for reducing their drinking, hence a clinical context.

amygdala reactivity compared to sham training with no clinical effects (for which it was not powered, see Supplementary Materials of the original publication).

A recent study (N=83) investigated the effect of four sessions of ApB-training vs. sham-training administered during alcohol detoxification (Manning et al., 2016). After training, fewer patients relapsed compared with sham-training (statistical trend for ITT-analysis and significant for per-protocol analysis). No differential effect was found on the standard ApB measure, but an effect was found in response accuracy rate in the ApB assessment task.

The final category of alcohol CBM-studies concerns online RCTs. The one published study (Wiers et al., 2015) contrasted effects of different types of CBM (varieties of ApB-training and AACTP) with sham-training in 314 self-identified problem drinkers who searched for help online. Participants who completed the post-test reported reduced alcohol consumption regardless of treatment allocation (no interaction between Time and Condition). Change in bias was not reported due to difficulties with the online assessment of the biases. This non-differential finding is corroborated by first results of online trials which have been presented at conferences (Van Deursen et al., 2016; Field and Jones, 2017), in which reduced drinking was reported across all conditions. One interesting question is whether this non-specific effect is related to a lack of efficiency in changing the bias when done online, or to the different treatment goal (abstinence vs. reduced drinking).

In conclusion, findings from RCTs of CBM in AUD mirror those in anxiety: clinically relevant effects when the bias is successfully changed in a clinical context (most consistently for ApB modification) and non-specific effects when the training takes place online.

Conclusion and Ways Forward

As argued above, when synthesizing research (either in a narrative review or a meta-analysis), it is crucial to differentiate between qualitatively different types of studies, which represent different phases of the EM-framework: experimental lab-studies aimed at

establishing causality which are typically performed in students not motivated to change, and RCTs with the targeted clinical population and an unequivocal behavior change goal (O'Connor et al., 2008; Sheeran et al., 2017). In the specific case of computerized interventions such as CBM, it is further important to establish the setting of the training, as an add-on intervention in a clinical setting or as a tool available online 24/7 accessible from everywhere (Table 1). When doing so, the conclusion is that CBM has small effects on drinking in students, but only if the bias has been successfully changed. However, these findings are short-lived and not directly clinically relevant (but do play a meaningful role within the EM-framework by informing subsequent RCTs). This does not mean that it is impossible that CBM could lead to clinically meaningful reductions in alcohol use in (heavy drinking) students when added to other interventions, such as motivational interviewing (Marlatt et al., 1998). Hence, CBM should not be regarded as an effective stand-alone intervention for problematically drinking students, but could still be tested as part of a more comprehensive intervention aimed at this group.

Regarding the potential of CBM in a clinical context, the scarce evidence so far indicates that CBM has potential as an add-on intervention to treatment for AUD. This does not mean that no improvements can be made. Cristea and colleagues (2016) called for sounder RCTs to settle the clinical effectiveness of CBM. While noting that some of the high risk of bias scores were misguided by the confusion of experimental lab-studies and RCTs, we concur that large trials testing the clinical efficacy of CBM in addiction are needed and that CBM paradigms can be improved and better integrated into clinical treatment. One potential way forward could be to integrate the cognitive-motivational part of CBT with CBM, which could also make it more meaningful for patients. Specifically, both the alcohol-related stimuli used for training and the behavioral alternatives can be personalized (Kopetz et al., 2017; Wiers et al., 2016). However, we do note that this would make patients' blinding

of condition allocation even harder as is typical in clinical research (including research on CBT). Finally, the scarce evidence so far has indicated that CBM online yields non-specific effects, but it is possible that relatively low cost personal guidance can improve efficacy as has been shown for online CBT, which could be combined with online CBM (Blankers et al., 2011; Riper et al., 2014).

In conclusion, when separating conceptually different types of studies, relating to different phases of intervention development, CBM holds promise for the identification of potential targets in students. Importantly, these should not be regarded as clinical studies, but as the justification for subsequent RCTs, in line with the general EM-framework. The data on CBM as an adjunct intervention for the treatment of AUD is sparse, but holds promise and should not be dismissed as a result of confusing experimental lab-studies and clinical RCTs. At a more general level, we believe this re-analysis demonstrates the importance of distinguishing experimental lab-studies aimed at revealing mechanisms underlying psychopathology and clinical RCTs as theoretically distinct phases of intervention development, in line with the general EM-framework. Recent NIH policies to consider all clinical and health-related research with a minimal intervention-component as clinical trials are therefore not only unpractical (see Reardon, 2017), but also conceptually questionable and may easily lead to invalid conclusions, as we believe the present case testifies.

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Table 1: Differences between Experimental Lab-studies and RCTs in CBM

Category of study	1. Experimental Lab-studies	2a. Online RCTs	2b. Clinical RCTs
1. Purpose of study	Establish causality	Test efficacy of CBM as stand-alone intervention	Test efficacy as addition to treatment as usual (TAU)
2. Participants' awareness of receiving intervention	Not informed that they may receive an intervention (or better: that their cognitive processes are manipulated)	Aware that they may receive intervention	Aware that they may receive intervention
3. Participants' motivation	Not motivated to change behaviour, motivated for course credits and/or financial reward	Motivated to change behavior	Motivated to change behavior
4. Participants' treatment goal	-	Typically reduction of use	Typically abstinence
5. Summary of outcomes	Effects on targeted bias, often without generalization. Short-lived effects on drinking.	Reduced drinking in all conditions.	Increased abstinence rates one year after treatment discharge (approximately 10%).

Table 2: Experimental Lab-Studies Manipulating Cognitive Biases for Alcohol

Reference	Participants	Which Cognitive Bias & Bias Change Outcome	Bias change?	Other Outcomes	Change Drinking?
Field & Eastwood, 2005	40 heavy social drinkers from students & staff	**AtB.** One group trained to attend alcohol, one group to avoid alcohol. AtB changed accordingly. Generalization not tested.	(+)?	Urge to drink increased in approach alcohol group as did beer consumption in taste test compared with avoid alcohol group.***	?***
Field et al, 2007	60 heavy social drinkers from students & staff	**AtB.** One group trained to attend, one to avoid alcohol and one group no change in contingency (50/50). AtB increased in attend alcohol, and decreased in avoid alcohol condition. But no generalization to untrained stimuli or tasks in avoid condition.	-	Craving increased in participants in approach alcohol group, but only when aware of contingencies during training	-
Schoenmakers et al., 2007	106 male heavy social drinkers from students	**AtB.** One group trained to avoid alcohol and one group no change in contingency (50/50). Trained participants had weaker AtB, but only for trained pictures (no generalization).	-	No effect on drink preference test (choose can with or without alcohol after experiment). No effect on craving.	-
Lee & Lee, 2015*	43 hazardously drinking students	**AtB.** One group trained to avoid alcohol, the other group received psychoeducation. Change in AtB assessed with eyetracking (lower dwell times on alcohol pictures).	+	No effects on behavior reported.	?
McGeary et al 2014**	41 students	**AtB.** Avoid alcohol or Continued Assessment control, eight sessions at home. Change in AtB not reported.	?	Stronger decrease in drinking in Avoid alcohol group.	+
Wiers et al, 2010	42 students	**ApB.** Participants trained to approach	+	Reduced drinking in taste-test in those	+***

		or avoid alcohol. Change in ApB, generalization to untrained stimuli and other task.		heavy drinkers who had been successfully trained to avoid alcohol.	
Lindgren et al 2015 st 1**	295 students	**ApB.** Three ApB training varieties: standard, general alcohol identity and personalized alcohol identity, each with own placebo control. No effects on alcohol-identity associations.	-	No effects on drinking behavior.	-
Lindgren et al 2015 st 2**	288 students	**ApB.** Same varieties of ApB training as in study 1. Effect on alcohol-ApB in original training, not in modified versions. No effects on alcohol-identity associations.	-	No effects on drinking behavior.	-
Sharbanee et al 2014*	74 students	**ApB** Focus on training mechanisms: three ApB training conditions (avoid alcohol, approach alcohol, sham (50/50) training). Change in ApB not in AtB.	+/-	No significant group differences in alcohol consumption in bogus taste-test. However, mediation analysis showed that change in alcohol consumption was mediated by change in ApB (but not in AtB) in the avoid-alcohol ApB condition.	-/+
Di Lemma & Field, 2017	120 students	**ApB and MemB. (selective inhibition) vs. control conditions**	Ap.B + Mem.B -	Both active groups drank less alcohol in bogus taste test.	+
Houben et al 2011	52 students	**MemB** (selective inhibition alcohol cues vs. no contingency). Significant effect of CBM on reduced positive beer associations.	+	Statistical trend of lower drinking in taste-test after CBM; Significant reduction in drinking during week after experiment.	+
Houben et al 2012	57 students	**MemB** (selective inhibition alcohol cues vs. no contingency). Significant effect of CBM on reduced positive beer associations.	+	Reduced drinking after CBM, mediated by reduction in positive beer associations. No effect on general inhibition (Stop task).	+
Jones et al 2013 st. 1	90 students	**MemB** (selective inhibition alcohol cues vs. no contingency). Training	+	Reduced drinking in taste-test, not week after experiment.	+

		motor inhibition with alcohol resulted in slowing after alcohol cues.			
Bowley et al, 2013*	59 students	**MemB** (selective inhibition alcohol cues vs. no contingency). No effect on memory associations.	-	Taste-test: Beer NoGo and Brief Alcohol Intervention less beer drunk than BeerGo condition. No effect on weekly drinking.	?***
Boendermaker et al., 2015, study 1	77 students	**MemB** (Selective Inhibition) in three varieties, two with gaming elements vs. placebo training). No change in memory bias.	-	No changes in drinking behavior. Social game version was rated as most motivating.	-
Smith et al 2017*	114 students	**MemB** (3 versions of selective inhibition compared with control). Change in alcohol-inhibition associations not recorded	?	No group differences in taste test or self-reported alcohol consumption in week after study	-
Houben et al, 2010a* Psychopharmacol	116 students	**MemB** (Evaluative Conditioning, EC). Two varieties of EC vs. Control (faces and objects). Negative objects EC resulted in more negative alcohol associations.	+	Reduced drinking in week after experiment after general objects EC.	+
Houben et al 2010b* Addictive Behaviours	88 students	**MemB (EC). Negative beer EC vs. no conditioning. Alcohol MemB not recorded.**	?	More negative attitudes towards beer, less craving and lower alcohol consumption in post-training bogus test and one week after training.	+
Woud et al, 2015*	74 students	**MemB** (interpretation bias training for alcohol-related or neutral scenarios (control).	-	Taste test with alcohol-free beer (no group effect) and week follow-up (no difference)	-

AtB = Attentional Bias for Alcohol; ApB = Approach Bias for Alcohol; MemB = Memory bias for Alcohol. We summarize bias change and behavioral change categorically (as in MacLeod & Clarke, 2015): + indicates the expected change, - no change, and ? not reported.

*Studies not included in Cristea et al 2016. We did not include studies in which CBM was combined with transcranial Direct Current Stimulation (tDCS, e.g. Den Uyl et al., 2015).

** Although McGeary et al (2014) did multiple sessions of training at home, participants were not recruited to change their drinking but for "a research study looking at the link between attention and alcohol use". We therefore classify it among experimental studies and not among RCTs. Similarly, in Lindgren et al (2015) students were "invited via email to participate in a study about cognitive processes and alcohol", and performed in two training sessions (or control) for monetary reward without therapeutic intentions.

*** As there was no neutral condition, it is not clear to what extent this was due to the increase in appetitive motivational processes in the approach alcohol condition.

Table 3: RCTs Manipulating Cognitive Biases for Alcohol

Reference	Participants	Which Cognitive Bias & Bias Change Outcome	**Bias change?**	Other Outcomes	**Change Drinking?**
Schoenmakers et al 2010	43 AUD patients	AtB (5 sessions on top of treatment). Training vs. placebo. Significant change in AtB (untrained stimuli)	+	No training effects on craving. Significantly longer time to relapse and earlier discharge rate in AtB group.	?
Cox et al., 2015	148 problem drinkers	AtB (4 sessions). Factorial design: AtB (yes/no) combined with Motivational intervention (yes/no). No AtB change reported, but program requires change for progression.	?	AtB produced short-lived reduction in drinking (3 months, not 6), Motivational intervention longer lasting effects (3 and 6 months).	+
Clerkin et al., 2016*	86 AUD/social anxiety patients	AtB (8 sessions, both alcohol and anxiety). Factorial design: AtB (real/placebo) for alcohol and/or theatening cues. Reduction in AtB in all conditions, no Time*Condition interaction.	-	Reduced qantity of drinking and AUD symptoms in all conditions at one-month follow-up, no time* condition interaction.	-
R. W. Wiers et al, 2011	214 AUD patients	ApB (4 sessions on top of treatment). 2 training conditions (explicit, implicit instruction), 2 control conditions (placebo training, nothing). Significant change in ApB, with generalization to alcohol-approach memory associations assessed with IAT	+	13% lower relapse rate in ApB (pooled) conditions	+
Eberl et al, 2013	509 AUD patients	ApB (12 sessions on top of treatment). Training vs No Training. Significant change in ApB.	+	9% lower relapse rate in ApB condition. Clinical effect mediated by change in ApB	+
Manning et al 2016*	83 AUD patients	ApB (4 sessions training/placebo during detox). Overall decrease of ApB across both conditions.Significantly more errors in pull-alcohol responses in ApB group	-/+	Marginally lower relapse rate in ApB group 2 weeks after training (intention to treat analysis; significant for training completers). Overall reduction in craving,	-/+

		and in push-alcohol responses in control group after training.		amount of drinking days and drinks per day, but not time*condition interaction.	
C. E. Wiers et al., 2015	36 AUD patients	ApB (6 sessions on top of treatment). Neurocognitive mechanism study (fMRI). Reduced amygdala reactivity to alcohol cues. No significant change in ApB.	-	Overall reduction in craving and arousal ratings of alcohol cues after training, but no time*condition interaction. No assessment of relapse rate (study not designed and powered for clinical outcome).	-
R. W. Wiers et al., 2015	314 problem drinkers	AtB/ApB (4 sessions; online stand-alone). Multiple training conditions (variants of ApB, AtB) vs sham training. No bias change reported.	?	Reduced drinking in all conditions, no interaction between Time and Condition.	-

AtB = Attentional Bias for Alcohol; ApB = Approach Bias for Alcohol; MemB = Memory bias for Alcohol. AUD = Alcohol Use Disorder.

* Studies not included in Cristea et al 2016. We summarize bias change and behavioral change categorically (as in MacLeod & Clarke, 2015): + indicates the expected change, - no change, and ? not reported.