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

Wiers, R.W.; Boffo, M.; Field, M.

Citation for published version (APA):
Wiers, R. W., Boffo, M., & Field, M. (2018). 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. *Journal of Studies on Alcohol and Drugs*, *79*(3), 333-343. https://doi.org/10.15288/jsad.2018.79.333

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

REINOUT W. WIERS, PH.D.,[a],* MARILISA BOFFO, PH.D.,[a] & MATT FIELD, PH.D.[b,c]

[a]Addiction Development and Psychopathology (ADAPT) lab, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands
[b]Department of Psychological Sciences, University of Liverpool, Liverpool, United Kingdom
[c]UK Centre for Tobacco and Alcohol Studies, Liverpool, United Kingdom

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 laboratory studies aimed at revealing psychological mechanisms underlying behavior and randomized controlled trials (RCTs) in clinical samples aimed at testing the efficacy of an intervention. **Method:** As an illustration, we reviewed the current state of the evidence on the efficacy of cognitive bias modification (CBM) interventions in alcohol use disorders. **Results:** A recent meta-analysis "cast serious doubts on the clinical utility of CBM interventions for addiction." That analysis combined experimental laboratory studies and RCTs. We demonstrated that, when studies are differentiated regarding study type (experimental laboratory study or RCT), mode of delivery (controlled experiment or Internet), and population (healthy volunteers or patients), the following effects are found: (a) short-lived effects of CBM on drinking behavior in experimental laboratory studies in students, but only when the bias is successfully manipulated; (b) small but robust effects of CBM on treatment outcome when administered as an adjunct to established treatments in clinical settings in RCTs with alcohol-dependent patients; and (c) nonspecific 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 behavioral therapy, and we conclude that disregarding the difference between experimental laboratory studies and RCTs can lead to invalid conclusions. (*J. Stud. Alcohol Drugs, 79,* 333–343, 2018)

RECENTLY, the U.S. 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. This new definition 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 laboratory studies aimed at exploring and testing psychological mechanisms underlying human behavior (typically in healthy volunteers) and randomized controlled trials (RCTs) aimed at testing the efficacy of an intervention in a clinical sample. This distinction is important both when designing and when 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 that 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 laboratory studies in students not motivated to change and RCTs with patients motivated to change. To highlight differences between types of studies, we start with a brief history of CBM in anxiety, in which it was first invented and applied to clinical groups, and we include lessons learned from this literature. We then outline the crucial difference between experimental studies and clinical trials using the 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.

Cognitive bias modification 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 with 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 & 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. MacLeod and Clarke (2015) argued that a distinction should be made between studies in which the targeted cognitive bias was successfully changed and those in which this was not the case (failed manipulation); they also noted that in those studies in which the bias was successfully changed effects were found on the emotional outcome measures, and in those studies in which the manipulation had failed this was not the case. Grafton and colleagues (2017) calculated Hedge's *g* for those studies from the original meta-analysis of Cristea et al. (2015), in which the bias was successfully changed and found medium effect sizes on emotional vulnerability but no effects on emotional vulnerability in studies in which the bias modification failed. In a reply, Cristea and colleagues (2017) argued that selecting studies based on the presence of change in the postulated mechanisms conflicts with current standards for evaluating psychotherapies. 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 individual patient data meta-analysis (including original data from 13 clinical studies) partly confirmed this (significant effects for diagnostic status, not for a social anxiety scale, Price et al., 2016), with training setting (clinical context or online) as one of the significant moderators (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 to establish effects on clinically relevant outcomes, it is crucial to test whether the targeted bias was successfully manipulated. Note that this criterion perfectly fits the experimental logic (Grafton et al., 2017) but has been criticized from a treatment evaluation perspective (Cristea et al., 2017), relating to the general theme of this article.

Cognitive bias modification 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 & 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 & Eastwood, 2005; Field et al., 2007; Schoenmakers et al., 2007; Wiers et al., 2010). Again, note that in some of these studies one experimental group was trained *toward* alcohol (something not done in RCTs for obvious ethical reasons), to test whether this resulted in increased drinking in a bogus taste test compared with a group trained away from alcohol. Results indicated that cognitive biases for alcohol could indeed be changed, with some short-lived effects on behavior (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 behavioral 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" (p.3). We have questioned the validity of this classification because of the qualitative difference between experimental laboratory 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 randomized controlled trials represent different phases of experimental medicine

Recently, a general EM framework was applied to the development of behavior change interventions (Sheeran et

TABLE 1.   Differences between experimental laboratory studies and randomized controlled trials (RCTs) in cognitive bias modification (CBM)

Category of study	1. Experimental laboratory studies	2a. Online RCTs	2b. Clinical RCTs
1. Purpose of study	Establish causality	Test efficacy of CBM as a stand-alone intervention	Test efficacy as addition to treatment as usual
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 an intervention	Aware that they may receive an intervention
3. Participants' motivation	Not motivated to change behavior, 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 1 year after treatment discharge (approximately 10%)

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, and (4) RCTs that investigate whether an intervention developed in the third stage leads to robust behavior change and whether this behavior change is mediated by changes in the psychological process.

Psychological experiments that experimentally manipulate cognitive biases 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., Houben et al., 2011a; Schoenmakers et al., 2007; Wiers et al., 2010). 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 is 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 (see 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 laboratory studies with nonclinical volunteers (Phase 2) would bias the applicability and generalizability of the results of CBM as a clinical intervention (Phase 4 of EM).

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, whereas for healthy student volunteers both are typically not the case. Based on the CBM-anxiety literature, we further distinguish between two subtypes of RCTs: (a) those in a clinical setting and (b) online studies in which self-identified problem drinkers receive CBM as a stand-alone intervention. These RCTs 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). Furthermore, the treatment goal is different: abstinence in in-clinic RCTs, whereas 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 they reported that the effect size was related to the 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, and (e) dealing with incomplete data. As noted, the Cochrane tool is the gold standard for the assessment of the risk of bias in RCTs (for which it is intended), but it must be interpreted with caution when applied to laboratory experiments. Cristea et al. (2016) did not do this. For example, the majority of laboratory studies were rated as unclear in risk of bias because these studies 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 laboratory studies and RCTs (see CONSORT guidelines, Boutron et al., 2017). Furthermore, 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 nonpharmacological interventions such as psychological interventions or surgery (Boutron et al., 2008; Schulz & 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 cognitive bias modification studies in the alcohol domain

Given the reasons outlined above to distinguish between experimental laboratory studies and RCTs and that there are only a few true RCTs, we present a narrative review of the current state of affairs. In doing so, we focus only on alcohol, for two reasons. First, the number of CBM studies is larger for alcohol than for smoking; and second, the CBM-smoking literature has recently been reviewed elsewhere (Mühlig et al., 2017). We included all alcohol-related studies that were addressed in Cristea et al. (2016) and added relevant studies that were not included (e.g., studies on evaluative conditioning) or that came out later. In line with MacLeod and Clarke (2015), we indicated for each study whether the targeted bias was successfully changed and whether effects on behavior were found. In line with the EM framework, we distinguished between experimental laboratory studies with student volunteers, in which effects on alcohol intake in the laboratory 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 is difficult to

compare with student volunteers who do not realize that 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 of one category of stimuli changes memory associations for that category (Houben et al., 2011a, 2012) but does not affect general inhibition capacity (Houben et al., 2012). Training of general executive functions is conceptually different: No specific cognitive bias is targeted, but instead the general cognitive ability to resolve interference and overcome biased information processing is targeted (Wiers et al., 2013). This type of training also requires many more sessions (see Houben et al., 2011b; 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: attention toward alcohol on 50% of pictures and away from alcohol on other 50%; 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); furthermore, no effects were found on drinking behavior. One study did report effects on AtB in a different task using eye tracking (Lee & Lee, 2015) but reported no effect on drinking. Last, one study reported effects on drinking frequency after repeated training in students (not motivated to change drinking) but did not report effects on 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 posttraining bogus

TABLE 2. Experimental lab studies manipulating cognitive biases for alcohol

Reference	Participants	Which cognitive bias and 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.[a]	?[a]
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)[b]	43 hazardously drinking students	**AtB.** One group trained to avoid alcohol; the other group received psychoeducation. Change in AtB assessed with eye tracking (lower dwell times on alcohol pictures).	+	No effects on behavior reported.	?
McGeary et al. (2014)[c]	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 or avoid alcohol. Change in ApB, generalization to untrained stimuli and other task.	+	Reduced drinking in taste test in those heavy drinkers who had been successfully trained to avoid alcohol.	+[a]
Lindgren et al. (2015) Study 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) Study 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)[b]	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.	ApB + MemB –	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).	+

Table continued

TABLE 2. *Continued*

Reference	Participants	Which cognitive bias and bias change outcome	Bias change?	Other outcomes	Change drinking
Jones et al. (2013) Study 1	90 students	**MemB** (selective inhibition alcohol cues vs. no contingency). Training motor inhibition with alcohol resulted in slowing after alcohol cues.	+	Reduced drinking in taste test, not during week after experiment.	+
Bowley et al. (2013)[b]	59 students	**MemB** (selective inhibition alcohol cues vs. no contingency). No effect on memory associations.	–	Taste test: In Beer NoGo and brief alcohol intervention less beer drunk than in BeerGo condition. No effect on weekly drinking.	?[a]
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)[b]	114 students	**MemB** (three 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)[b] *Psychopharmacology*	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)[b] *Addictive Behaviors*	88 students	**MemB (EC)**. Negative beer EC vs. no conditioning. Alcohol MemB not recorded.	?	More negative attitudes toward beer, less craving and lower alcohol consumption in post-training bogus test and 1 week after training.	+
Woud et al. (2015)[b]	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).	–

Notes: We summarize bias change and behavioral change categorically (as in MacLeod & Clarke, 2015): + indicates the expected change, – indicates no change, and ? indicates not reported. AtB = attentional bias for alcohol; ApB = approach bias for alcohol; MemB = memory bias for alcohol; CBM = cognitive bias modification. [a]Because there was no neutral condition, it is not clear to what extent this was the result of the increase in appetitive motivational processes in the approach-alcohol condition. [b]Studies not included in Cristea et al.(2016); we did not include studies in which CBM was combined with transcranial direct current stimulation (e.g., Den Uyl et al., 2017). [c]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." (p. 560) We therefore classify it among experimental studies and not among randomized controlled trials. Similarly, in Lindgren et al. (2015), students were "invited via email to participate in a study about cognitive processes and alcohol" (p. 7) and performed in two training sessions (or control) for monetary reward without therapeutic intentions.

taste test in the alcohol-avoid ApB condition (Sharbanee et al., 2014). A recent study tested effects of ApB modification versus selective inhibition (discussed below) versus their respective control conditions (Di Lemma & 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/No-Go task: In the experimental condition, alcohol pictures are consistently paired with No-Go (stop) cues, whereas in the control condition there is no such pairing. Two studies by Houben and colleagues (2011a, 2012) found a generalized effect on memory associations (assessed with an implicit association test [IAT]) and an effect on reduced drinking in the week after the experiment. Other studies (Boendermaker et al., 2015; Bowley et al., 2013) found no change in memory bias or 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. Two studies used an alcohol variety of the Stop-signal task (Jones & Field, 2013; Smith et al., 2017). Two studies used evaluative conditioning (Houben et al., 2010a, 2010b), 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, 2010b; Jones & Field, 2013) but not when the bias was not successfully changed (Woud et al., 2015). Note that in some studies change in bias was not reported (e.g., Smith et al., 2017).

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 the general pattern of results in anxiety (MacLeod & 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., 2016): 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

Table 3 summarizes the results. 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 eight 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 the training condition (no Time × Condition interaction). Cox and colleagues (2015) combined AtB training and motivational enhancement.[1] The training paradigm used was the Alcohol Attention-Control Training Program (AACTP), which had shown promise in an earlier uncontrolled study in which problem drinkers reduced drinking compared with baseline (Fadardi & Cox, 2009). The AACTP uses training varieties of pictorial Stroop tests and increasing levels of difficulty to motivate participants. In Cox et al. (2015)'s study, the AACTP and motivational enhancement could both be present or absent (2 × 2 design). The AACTP led to reduced drinking in the short term (3 months but not 6 months after the intervention). Motivational enhancement reduced drinking 3 months and 6 months after the intervention.

---

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

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 a 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 with no training, resulted in a 9% lower relapse rate at 1-year follow-up, and this effect was mediated by the change in ApB (Eberl et al., 2013). Moderation was also found (stronger change of bias in patients with strong alcohol ApB before training).

Cristea and colleagues (2016) included one other study of ApB training in AUD patients, a functional magnetic resonance imaging 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 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 versus 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 the response accuracy rate in the ApB assessment task.

The final category of alcohol CBM studies concerns online RCTs. The one published study (R.W. 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 posttest reported reduced alcohol consumption regardless of treatment allocation (no interaction between Time and Condition). Change in bias was not reported because of difficulties with the online assessment of the biases. This nondifferential finding is corroborated by preliminary results of online trials that have been presented at conferences (Field & Jones, 2017; Deursen et al., 2016), in which reduced drinking was reported across all conditions. One interesting question is whether this nonspecific 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 nonspecific effects when the training takes place online.

TABLE 3.   Randomized controlled trials manipulating cognitive biases for alcohol

Reference	Participants	Which cognitive bias and bias change outcome	Bias change?	Other outcomes	Change drinking?
Schoenmakers et al. (2010)	43 AUD patients	AtB (five 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 (four 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 produced longer lasting effects (3 and 6 months).	+
Clerkin et al. (2016)[a]	86 AUD/social anxiety patients	AtB (eight 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 1-month follow-up, no Time × Condition interaction.	−
Wiers et al. (2011)	214 AUD patients	ApB (four sessions on top of treatment). Two training conditions (explicit, implicit instruction), two 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)[a]	83 AUD patients	ApB (four sessions training/ placebo during detox). Overall decrease of ApB across both conditions. Significantly more errors in pull-alcohol responses in ApB group and in push-alcohol responses in control group after training.	−/+	Marginally lower relapse rate in ApB group 2 weeks after training (intention to treat analysis; significant for training completers). Overall reduction in craving, amount of drinking days and drinks per day but no significant Time × Condition interaction.	−/+
C. W. Wiers et al. (2015)	36 AUD patients	ApB (six 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 (four sessions; online stand-alone). Multiple training conditions (variants of ApB, AtB) vs. sham training. No bias change reported.	?	Reduced drinking in all conditions, no Time × Condition interaction.	−

Notes: We summarize bias change and behavioral change categorically (as in MacLeod & Clarke, 2015): + indicates the expected change, – no change, and ? not reported. AtB = attentional bias for alcohol; AUD = alcohol use disorder; ApB = approach bias for alcohol. [a]Studies not included in Cristea et al. (2016).

Conclusion and ways forward

As argued earlier, 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 laboratory 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 are not directly clinically relevant (but they 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 students who drink problematically, but it 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 was misguided by the confusion of experimental laboratory 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). Last, the scarce evidence so far has indicated that CBM online yields nonspecific 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, such studies should not be regarded as clinical trials, 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 are sparse but hold promise and should not be dismissed as a result of confusing experimental laboratory studies and clinical RCTs. At a more general level, we believe that this re-analysis demonstrates the importance of distinguishing experimental laboratory 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.

References

Allom, V., Mullan, B., & Hagger, M. (2016). Does inhibitory control training improve health behaviour? A meta-analysis. *Health Psychology Review, 10,* 168–186. doi:10.1080/17437199.2015.1051078

Amir, N., Beard, C., Burns, M., & Bomyea, J. (2009). Attention modification program in individuals with generalized anxiety disorder. *Journal of Abnormal Psychology, 118,* 28–33. doi:10.1037/a0012589

Blankers, M., Koeter, M. W. J., & Schippers, G. M. (2011). Internet therapy versus internet self-help versus no treatment for problematic alcohol use: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 79,* 330–341. doi:10.1037/a0023498

Boendermaker, W. J., Boffo, M., and Wiers, R. W. (2015). Exploring elements of fun to motivate youth to do cognitive bias modification. *Games for Health Journal, 4,* 434–443. doi:10.1089/g4h.2015.0053

Boutron, I., Altman, D., Moher, D., Schulz, K. F., & Ravaud, P. (2017). CONSORT Statement for randomized trials of nonpharmacologic treatments: A 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Annals of Internal Medicine, 167,* 40–47. doi:10.7326/M17-0046

Boutron, I., Moher, D., Altman, D. G., Schulz, K. F., & Ravaud, P., & the CONSORT Group. (2008). Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: Explanation and elaboration. *Annals of Internal Medicine, 148,* 295–309. doi:10.7326/0003-4819-148-4-200802190-00008

Bowley, C., Faricy, C., Hegarty, B., Johnstone, S. J., Smith, J. L., Kelly, P. J., & Rushby, J. A. (2013). The effects of inhibitory control training on alcohol consumption, implicit alcohol-related cognitions and brain electrical activity. *International Journal of Psychophysiology, 89,* 342–348. doi:10.1016/j.ijpsycho.2013.04.011

Clerkin, E. M., Magee, J. C., Wells, T. T., Beard, C., & Barnett, N. P. (2016). Randomized controlled trial of attention bias modification in a racially diverse, socially anxious, alcohol dependent sample. *Behaviour Research and Therapy, 87,* 58–69. doi:10.1016/j.brat.2016.08.010

Cox, W. M., Fadardi, J. S., Hosier, S. G., & Pothos, E. M. (2015). Differential effects and temporal course of attentional and motivational training on excessive drinking. *Experimental and Clinical Psychopharmacology, 23,* 445–454. doi:10.1037/pha0000038

Cristea, I. A., Kok, R. N., & Cuijpers, P. (2015). Efficacy of cognitive bias modification interventions in anxiety and depression: Meta-analysis. *British Journal of Psychiatry, 206,* 7–16. doi:10.1192/bjp.bp.114.146761

Cristea, I. A., Kok, R. N., & Cuijpers, P. (2016). The effectiveness of cognitive bias modification interventions for substance addictions: A meta-analysis. *PLoS ONE, 11,* e0162226. doi:10.1371/journal.pone.0162226

Cristea, I. A., Kok, R. N., & Cuijpers, P. (2017). Invited commentary on . . . Confusing procedures with process in cognitive bias modification research. *British Journal of Psychiatry, 211,* 272–273. doi:10.1192/bjp.bp.117.200972

Den Uyl, T. E., Gladwin, T. E., Rinck, M., Lindenmeyer, J., & Wiers, R. W. (2017). A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. *Addiction Biology, 22,* 1632–1640. doi:10.1111/adb.12463

Deursen van, D. S., Salemink, E., & Wiers, R. W. (2016). *Effectiveness of online cognitive bias modification for problem drinkers: Preliminary results.* Oral communication at the 8thWorld Congress of Behavioural and Cognitive Therapies, Melbourne, Australia.

Di Lemma, L. C. G., & Field, M. (2017). Cue avoidance training and inhibitory control training for the reduction of alcohol consumption: A comparison of effectiveness and investigation of their mechanisms of action. *Psychopharmacology, 234,* 2489–2498. doi:10.1007/s00213-017-4639-0

Eberl, C., Wiers, R. W., Pawelczack, S., Rinck, M., Becker, E. S., & Lindenmeyer, J. (2013). Approach bias modification in alcohol dependence: Do clinical effects replicate and for whom does it work best? *Developmental Cognitive Neuroscience, 4,* 38–51. doi:10.1016/j.dcn.2012.11.002

Fadardi, J. S., & Cox, W. M. (2009). Reversing the sequence: Reducing alcohol consumption by overcoming alcohol attentional bias. *Drug and Alcohol Dependence, 101,* 137–145. doi:10.1016/j.drugalcdep.2008.11.015

Field, M., & Cox, W. M. (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence, 97,* 1–20. doi:10.1016/j.drugalcdep.2008.03.030

Field, M., Duka, T., Eastwood, B., Child, R., Santarcangelo, M., & Gayton, M. (2007). Experimental manipulation of attentional biases in heavy drinkers: Do the effects generalise? *Psychopharmacology, 192,* 593–608. doi:10.1007/s00213-007-0760-9

Field, M., & Eastwood, B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. *Psychopharmacology, 183,* 350–357. doi:10.1007/s00213-005-0202-5

Field, M., & Jones, A. (2017). *Randomized controlled trial of inhibitory control training for alcohol use disorders.* Denver, CO: Research Society on Alcoholism.

Field, M., Jones, A., & Christiansen, P. (2016). Questionable classification of studies and choice of outcome measures [comment to Cristea et al. (2016). The effectiveness of cognitive bias modification interventions for substance addictions: A meta-analysis. *PLoS One, 11,* e0162226. doi:10.1371/journal.pone.0162226]. Retrieved from http://journals.plos.org/plosone/article/comment?id=10.1371/annotation/9266868f-9ddd-4b2c-a899-aa4cf3cfb7f0

Grafton, B., MacLeod, C., Rudaizky, D., Holmes, E. A., Salemink, E., Fox, E., & Notebaert, L. (2017). Confusing procedures with process when appraising the impact of cognitive bias modification (CBM) on emotional vulnerability: A response to Cristea et al. (2015). *British Journal of Psychiatry, 211,* 266–271. doi:10.1192/bjp.bp.115.176123

Heeren, A., Mogoa e, C., Philippot, P., & McNally, R. J. (2015). Attention bias modification for social anxiety: A systematic review and meta-analysis. *Clinical Psychology Review, 40,* 76–90. doi:10.1016/j.cpr.2015.06.001

Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., . . . Sterne, J. A. C., & the Cochrane Bias Methods Group, & the Cochrane Statistical Methods Group. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343,* d5928. doi:10.1136/bmj.d5928

Houben, K., Havermans, R. C., Nederkoorn, C., & Jansen, A. (2012). Beer à no-go: Learning to stop responding to alcohol cues reduces alcohol intake via reduced affective associations rather than increased response inhibition. *Addiction, 107,* 1280–1287. doi:10.1111/j.1360-0443.2012.03827.x

Houben, K., Havermans, R. C., & Wiers, R. W. (2010a). Learning to dislike alcohol: Conditioning negative implicit attitudes toward alcohol and its effect on drinking behavior. *Psychopharmacology, 211,* 79–86. doi:10.1007/s00213-010-1872-1

Houben, K., Schoenmakers, T., & Wiers, R. W. (2010b). I didn't feel like drinking but I don't know why: The effects of evaluative conditioning on alcohol-related attitudes, craving and behavior. *Addictive Behaviors, 35,* 1161–1163. doi:10.1016/j.addbeh.2010.08.012

Houben, K., Nederkoorn, C., Wiers, R. W., and Jansen, A. (2011a). Resisting temptation: Decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug and Alcohol Dependence, 116,* 132–136. doi:10.1016/j.drugalcdep.2010.12.011

Houben, K., Wiers, R. W., & Jansen, A. (2011b). Getting a grip on drinking behavior: Training working memory to reduce alcohol abuse. *Psychological Science, 22,* 968–975. doi:10.1177/0956797611412392

Jones, A., Di Lemma, L. C. G., Robinson, E., Christiansen, P., Nolan, S., Tudur-Smith, C., & Field, M. (2016). Inhibitory control training for appetitive behaviour change: A meta-analytic investigation of mechanisms of action and moderators of effectiveness. *Appetite, 97,* 16–28. doi:10.1016/j.appet.2015.11.013

Jones, A., & Field, M. (2013). The effects of cue-specific inhibition training on alcohol consumption in heavy social drinkers. *Experimental and Clinical Psychopharmacology, 21,* 8–16. doi:10.1037/a0030683

Kopetz, C., MacPherson, L., Mitchell, A. D., Houston-Ludlam, A. N., & Wiers, R. W. (2017). A novel training approach to activate alternative behaviors for smoking in depressed smokers. *Experimental and Clinical Psychopharmacology, 25,* 50–60. doi:10.1037/pha0000108

Lee, S., and Lee, J. H. (2015). The effect of automatic attentional bias modification on alcohol ambivalence. *Addictive Behaviors, 46,* 58–64. doi:10.1016/j.addbeh.2015.03.010

Lindgren, K. P., Wiers, R. W., Teachman, B., Gasser, M. L., Westgate, E. C., Cousijn, J., Enkema, M., & Neighbors, C. (2015). Attempted Training of Alcohol Approach and Drinking Identity Associations in US Undergraduate Drinkers: Null Results from Two Studies. PlosOne, 10(8), e0134642. doi:10.1371/journal.pone.0134642

Linetzky, M., Pergamin-Hight, L., Pine, D. S., & Bar-Haim, Y. (2015). Quantitative evaluation of the clinical efficacy of attention bias modification treatment for anxiety disorders. *Depression and Anxiety, 32,* 383–391. doi:10.1002/da.22344

MacLeod, C., & Clarke, P. J. F. (2015). The attentional bias modification approach to anxiety intervention. *Clinical Psychological Science, 3,* 58–78. doi:10.1177/2167702614560749

MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., & Holker, L. (2002). Selective attention and emotional vulnerability: Assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of Abnormal Psychology, 111,* 107–123. doi:10.1037/0021-843X.111.1.107

Manning, V., Staiger, P. K., Hall, K., Garfield, J. B. B., Flaks, G., Leung, D., . . . Verdejo-Garcia, A. (2016). Cognitive bias modification training during inpatient alcohol detoxification reduces early relapse: A randomized controlled trial. *Alcoholism: Clinical and Experimental Research, 40,* 2011–2019. doi:10.1111/acer.13163

Marlatt, G. A., Baer, J. S., Kivlahan, D. R., Dimeff, L. A., Larimer, M. E., Quigley, L. A., . . . Williams, E. (1998). Screening and brief intervention for high-risk college student drinkers: Results from a 2-year follow-up assessment. *Journal of Consulting and Clinical Psychology, 66,* 604–615. doi:10.1037/0022-006X.66.4.604

McGeary, J. E., Meadows, S. P., Amir, N., and Gibb, B. E. (2014). Computer-delivered, home-based, attentional retraining reduces drinking behavior in heavy drinkers. *Psychology of Addictive Behaviors, 28,* 559–62.doi:10.1037/a0036086

Mühlig, S., Paulick, J., Lindenmeyer, J., Rinck, M., Cina, R., & Wiers, R. W. (2017). Applying the "Cognitive Bias Modification" concept to smoking cessation. *Sucht, 62,* 333–354. doi:10.1024/0939-5911/a000454

O'Connor, D., Green, S., & Higgins, J. P. T. (2008). Defining the review question and developing criteria for including studies. In J. P. T. Higgins & S. Green (Eds.), *Cochrane handbook for systematic reviews of interventions: Cochrane book series* (pp. 81–95). Hoboken, NJ: Wiley. doi:10.1002/9780470712184.ch5

Price, R. B., Wallace, M., Kuckertz, J. M., Amir, N., Graur, S., Cummings, L., Popa, P., . . . Bar-Haim, Y. (2016). Pooled patient-level meta-analysis of children and adults completing a computer-based anxiety intervention targeting attentional bias. *Clinical Psychology Review, 50,* 37–49. doi:10.1016/j.cpr.2016.09.009

Reardon, S. (2017). Brain researchers in uproar over NIH clinical-trials policy. *Nature.* doi:10.1038/nature.2017.22550

Riper, H., Blankers, M., Hadiwijaya, H., Cunningham, J., Clarke, S., Wiers, R., . . . Cuijpers, P. (2014). Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: A meta-analysis. *PLoS ONE, 9,* e99912. doi:10.1371/journal.pone.0099912

Rooke, S. E., Hine, D. W., & Thorsteinsson, E. B. (2008). Implicit cognition and substance use: A meta-analysis. *Addictive Behaviors, 33,* 1314–1328. doi:10.1016/j.addbeh.2008.06.009

Schoenmakers, T. M., de Bruin, M., Lux, I. F. M., Goertz, A. G., Van Kerkhof, D. H., & Wiers, R. W. (2010). Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug and Alcohol Dependence, 109,* 30–36. doi:10.1016/j.drugalcdep.2009.11.022

Schoenmakers, T., Wiers, R. W., Jones, B. T., Bruce, G., & Jansen, A. T. M. (2007). Attentional re-training decreases attentional bias in heavy drinkers without generalization. *Addiction, 102,* 399–405. doi:10.1111/j.1360-0443.2006.01718.x

Schulz, K. F., & Grimes, D. A. (2002). Allocation concealment in randomised trials: Defending against deciphering. *The Lancet, 359,* 614–618. doi:10.1016/S0140-6736(02)07750-4

Sharbanee, J. M., Hu, L., Stritzke, W. G. K., Wiers, R. W., Rinck, M., & MacLeod, C. (2014). The effect of approach/avoidance training on alcohol consumption is mediated by change in alcohol action tendency. *PLoS ONE, 9,* e85855. doi:10.1371/journal.pone.0085855

Sheeran, P., Klein, W. M. P., & Rothman, A. J. (2017). Health behavior change: Moving from observation to intervention. *Annual Review of Psychology, 68,* 573–600. doi:10.1146/annurev-psych-010416-044007

Smith, J. L., Dash, N. J., Johnstone, S. J., Houben, K., & Field, M. (2017). Current forms of inhibitory training produce no greater reduction in drinking than simple assessment: A preliminary study. *Drug and Alcohol Dependence, 173,* 47–58. doi:10.1016/j.drugalcdep.2016.12.018

Spencer, S. J., Zanna, M. P., & Fong, G. T. (2005). Establishing a causal chain: Why experiments are often more effective than mediational analyses in examining psychological processes. *Journal of Personality and Social Psychology, 89,* 845–851. doi:10.1037/0022-3514.89.6.845

Wiers, C. E., Stelzel, C., Gladwin, T. E., Park, S. Q., Pawelczack, S., Gawron, C. K., . . . Bermpohl, F. (2015). Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. *American Journal of Psychiatry, 172,* 335–343. doi:10.1176/appi.ajp.2014.13111495

Wiers, R. W. (2016, September 21). Cognitive bias modification does hold promise in the treatment of addiction: A commentary on Cristea et al. 2016 PlosOne [comment to Cristea et al. (2016). The effectiveness of cognitive bias modification interventions for substance addictions: A meta-analysis. *PLoS One, 11,* e0162226. doi:10.1371/journal.pone.0162226]. Retrieved from http://journals.plos.org/plosone/article/comment?id=10.1371/annotation/8cde1186-7802-4dd5-b686-d4a66c84fb84

Wiers, R. W., Becker, D., Holland, R., Moggi, F., Lejuez, C. W., & Yield, A. (2016). Cognitive motivational processes underlying addiction treatment. In C. E. Kopetz & C. W. Lejuez (Eds.), *Addiction* (pp. 201–236). New York, NY: Psychology Press.

Wiers, R. W., Eberl, C., Rinck, M., Becker, E. S., & Lindenmeyer, J. (2011). Retraining automatic action tendencies changes alcoholic patients approach bias for alcohol and improves treatment outcome. *Psychological Science, 22,* 490–497. doi:10.1177/0956797611400615

Wiers, R. W., Gladwin, T. E., Hofmann, W., Salemink, E., & Ridderinkhof, K. R. (2013). Cognitive bias modification and cognitive control training in addiction and related psychopathology: Mechanisms, clinical perspectives, and ways forward. *Clinical Psychological Science, 1,* 192–212. doi:10.1177/2167702612466547

Wiers, R. W., Houben, K., Fadardi, J. S., van Beek, P., Rhemtulla, M., and Cox, W. M. (2015). Alcohol cognitive bias modification training for problem drinkers over the web. *Addictive Behaviors, 40,* 21–26. doi:10.1016/j.addbeh.2014.08.010

Wiers, R. W., Rinck, M., Dictus, M., & van den Wildenberg, E. (2009). Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1 G-allele. *Genes, Brain, & Behavior, 8,* 101–106. doi:10.1111/j.1601-183X.2008.00454.x