# Approach-Bias Retraining and Other Training Interventions as Add-On in the Treatment of AUD Patients



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**Abstract** In the past two decades, a variety of cognitive training interventions have been developed to help people overcome their addictive behaviors. Conceptually, it is important to distinguish between programs in which reactions to addictionrelevant cues are trained (varieties of cognitive bias modification, CBM) and programs in which general abilities are trained such as working memory or mindfulness. CBM was first developed to study the hypothesized causal role in mental disorders: by directly manipulating the bias, it was investigated to what extent this influenced disorder-relevant behavior. In these proof-of-principle studies, the bias was temporarily modified in volunteers, either temporarily increased or decreased, with corresponding effects on behavior (e.g., beer consumption), in case the bias was successfully manipulated. In subsequent clinical randomized controlled trials (RCTs), training (away from the substance vs. sham training) was added to clinical treatment. These studies have demonstrated that CBM, as added to treatment, reduces relapse with a small effect of about 10% (similar effect size as for medication, with the strongest evidence for approach-bias modification). This has not been found for general ability training (e.g., working memory training), although effects on other psychological functions have been found (e.g., impulsivity). Mindfulness also has been found to help people overcome addictions, and different from CBM, also as stand-alone intervention. Research on (neuro-)cognitive mechanisms underlying approach-bias modification has pointed to a new perspective in which automatic inferences rather than associations are influenced by training, which has led to the development of a new variety of training: ABC training.

**Keywords** Addiction  $\cdot$  Alcohol use disorder  $\cdot$  Approach bias  $\cdot$  Approach bias retraining  $\cdot$  Cognitive-bias modification  $\cdot$  Cognitive training  $\cdot$  Mindfulness  $\cdot$  Treatment  $\cdot$  Working memory training

#### **Abbreviations**

AAT Approach-avoidance task

ABC New variety of cognitive-bias modification, with personalized

antecedents, behavioral alternatives, and consequences

ApB Approach bias

ApBM Approach bias modification

AtB Attentional bias

AtBM Attentional bias modification

AUD Alcohol use disorder

CBM Cognitive-bias modification (family of interventions, aimed at directly

targeting different cognitive biases, including AtB, ApB, and memory

biases

CBT Cognitive behavior therapy
EC Evaluative conditioning
IAT Implicit association test
mPFC Medial prefrontal cortex
RCT Randomized controlled trial

RT Reaction time

SUD Substance use disorder

tDCS Transcranial direct current stimulation (form of neuromodulation)
TMS Transcranial magnetic stimulation (form of neuromodulation)

WM Working memory

#### 1 Introduction

This chapter focuses on (neuro)cognitive training as a therapeutic add-on in the treatment of alcohol use disorders (AUDs). After a series of successful randomized controlled trials (RCTs), one specific type of training, approach-bias retraining (Eberl et al. 2013; Manning et al. 2021; Rinck et al. 2018; Salemink et al. 2021; Wiers et al. 2011), has been added as suggested additions to the treatment of AUD in

the clinical guidelines in the countries where the supportive large RCTs took place (Haber 2021; Kiefer et al. 2021 Australia and Germany, respectively). However, approach-bias re-training is only one instance of a larger family of training interventions, called cognitive-bias modification (CBM) interventions. These interventions target the re-training of relatively automatic or impulsive reactions to addiction-related stimuli referred to as "cognitive biases." Other types of training interventions do not use substance-related cues and target more general functions, such as working memory training and mindfulness training (see Fig. 1); these will be briefly discussed in Sect. 5.

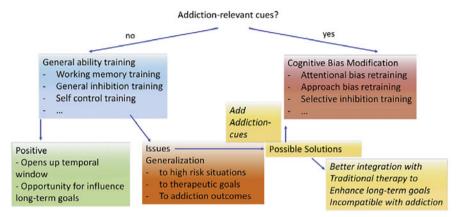
The first section discusses the background of different types of CBM; the second reviews the current state of the evidence for the effectiveness of CBM as an add-on to the treatment of AUD, with a brief note on the current (absence of) evidence as stand-alone intervention. The third section reviews other forms of targeted training as an add-on to the treatment of AUD, forms that do not fall under the umbrella of CBM. The fourth section reviews recent work on underlying (neuro-)cognitive mechanisms in CBM, with an emphasis on approach-bias retraining. In the fifth section, we briefly review two instances of the other type of more general cognitive training that has been used in (alcohol) addiction: working memory training and mindfulness meditation. In the sixth section, we sketch out new avenues to improve targeted training as an add-on to the treatment of AUD and other addictions.

### 2 Cognitive Bias Modification, Background and Taxonomy

In CBM, different types of cognitive biases have been targeted. Most studies target one of three cognitive biases, namely biases in attention (attentional bias modification, or AtBM), biases in action tendencies (in addiction, typically a tendency to approach addiction cues, hence approach bias modification, or ApBM), or biases in (evaluative) memory (see for an early review: Wiers et al. 2013b). Note that in the broad field of internalizing disorders (varieties of anxiety and mood disorders), another type of cognitive bias has often been successfully targeted using CBM: interpretation bias (Hallion and Ruscio 2011; Krebs et al. 2018). This has not been done as an add-on to treatment in addiction, although there is preliminary work that interpretation biases can also be found in AUD patients, but were difficult to modify in social drinkers (Woud et al. 2014, 2015). In healthy subjects with high scores on social anxiety and drinking, there is initial evidence of comorbidity-specific interpretation biases (Chow et al. 2018). In some sense, the recently developed novel ABC training (Wiers et al. 2020), discussed in Sect. 6 below, bears some resemblance to interpretation bias retraining, and could also be used to address biases of

<sup>&</sup>lt;sup>1</sup>Note that both attentional bias modification and approach bias modification have sometimes been abbreviated to ABM, which is unhandy for obvious reasons; therefore, we have argued to consistently use AtBM and ApBM (Rinck et al. 2018).

#### Cognitive training in addiction



**Fig. 1** A classification scheme concerning different types of training used in addiction. The major division is between training varieties that use addiction-related stimuli, in order to change stimulus-related reactions (i.e., aspects of cue reactivity) and varieties of training that do not use addiction-related stimuli, which aim to change general processes, such as working memory, self-control, or inhibition. Reproduced with permission from Wiers (2018)

specific comorbidity subgroups. In the following, we will introduce the three main types of CBM used in (alcohol) addiction: AtBM, ApBM, and varieties of CBM targeting (evaluative) memories.

### 2.1 Attentional Bias (AtB)

Biases in attention may play an important role in many mental disorders, including anxieties (Bar-Haim et al. 2007), mood disorders (Peckham et al. 2010), and addictions (Field and Cox 2008, but see Field et al. 2016 for a more critical appraisal). The most commonly used tasks to assess attentional biases in addiction have been the addiction-Stroop task (Cox et al. 2006), and the visual or dot-probe task (Field and Cox 2008). The addiction-Stroop assesses whether participants are relatively slow in color-naming words that relate to an addictive behavior. In the dot-probe task, participants see two stimuli presented simultaneously on the screen (in addiction, typically two pictures), after which one of the two is replaced with a probe to which a participant has to react (e.g., a small arrow pointing up or down, which has to be indicated by the participant). When the participant is quicker and more accurate to react to probes replacing one category of pictures (e.g., alcohol), than the contrast category (e.g., non-alcoholic drinks), this is taken as an indication of an attentional bias for alcohol (see Fig. 2 for an example). Although the dot-probe task is intuitive and easy to use, the reliability is poor (e.g., Ataya et al. 2012). More reliable (but less frequently used) are eye-movement measures (Field et al. 2009),

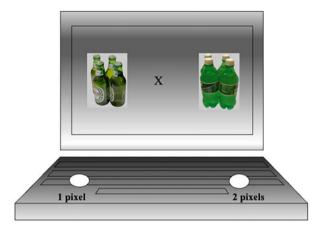


Fig. 2 In the dot-probe assessment task, two stimuli are shown simultaneously (here one picture of drinks with alcohol and one of drinks without alcohol), followed by the probe (one or two pixels) which replaces one of the two pictures, to which the participant responds (e.g., left if the probe is a single pixel and right if it concerns two pixels). The AtB is derived from the difference in RT between responses where the probe replaces alcohol vs. non-alcoholic drinks. In an assessment task, probes replace alcoholic and non-alcoholic drinks equally often. In a training, this is changed; probes occur either more frequently after alcohol (in proof-of-principle studies) to test if this increases the desire to drink or more frequently behind non-alcoholic drinks (also used in clinical context)

which can demonstrate a stimulus category participants preferentially divert attention to or dwell upon. Recently, a new behavioral measure has been developed that indirectly assesses attentional capture (without assessment of eye movements): the dual-probe task. In this task, participants see two video-streams, one disorder-relevant and one irrelevant (e.g., ads for alcohol vs. non-alcoholic drinks), upon which occasionally unique probes are projected that participants have to identify, revealing which stream they were looking at (Cahill et al. 2021; Grafton et al. 2021; MacLeod et al. 2019; Wiechert et al. 2021). A recent study (Wiechert et al. 2021), assessing attentional capture by ads for alcoholic vs. non-alcohol drinks in undergraduate volunteers, predicted habitual drinking, subsequent drinking in a taste test and increased craving in this situation, and importantly, demonstrated excellent reliability (0.90), which starkly contrasts with the poor-to-modest reliabilities of the dot probe (typically around 0.30).

An attentional bias for substance-related cues has been demonstrated across many studies (review: Field and Cox 2008), although there have also been inconsistencies (Field et al. 2016). This is not unique for addiction; an attentional bias (AtB) for disorder-related stimuli has been reported in many forms of psychopathology. Importantly, more fine-grained analyses have revealed differences in the time course of AtB, with most evidence supporting the perspective that in anxiety disorders, threat stimuli grab attention (short time course, attentional engagement). In the dot-probe task, this is assessed with a brief stimulus duration, for example of 150 ms for the pairs of stimuli, followed by the probe. In anxiety, the quick

attentional deployment is typically followed by avoidance, the so-called vigilanceavoidance pattern (Mogg et al. 1995). In contrast, in depression and related disorders, relevant negative stimuli tend to capture attention, which implies issues with disengagement (longer time course). In the dot-probe task, this is measured with longer presentation times of the stimuli, where an AtB is interpreted as an attentional disengagement problem (Koster et al. 2005; Oehlberg et al. 2012). It is as-yet unclear whether AtB in addiction resembles more the engagement AtB typically found in anxieties, or the difficulties with disengagement AtB typically found in mood disorders. There is some evidence in support of only relatively late processes (and hence disengagement problems), both in heavy drinkers (Field et al. 2004) and in heroin-addicted patients (Franken et al. 2000). Yet, other studies found evidence for early engagement in AUD (Ingjaldsson et al. 2003; Noël et al. 2006) and opioid dependence (Frankland et al. 2016) An EEG study (with good time resolution) detected an early component (N1) in attentional responses to alcohol cues in AUD patients (Dickter et al. 2014). Hence, the nature of AtB in addiction could differ per stage of addiction (e.g., disengagement problems in early stages of addiction and engagement in severe addiction) and per addictive behavior. Although this topic is relatively understudied, it is an important line of research as it could inform effective ways to modify AtB. Notably, new measures are currently under development to assess AtB in a more reliable way (Gladwin et al. 2020; Wiechert et al. 2021). This is important because current measures are not reliable enough to assess AtB at an individual level (the level where clinical decisions are made), and the low reliability also makes it difficult to assess whether procedures aimed at modifying AtB (varieties of AtBM) succeed in changing the bias.

Finally, there is recent work relating substance AtB in (alcohol) addiction to a general AtB for reward cues, or more precisely the extent to which participants are distracted by general reward cues, based on sign-tracking in animal paradigms (Albertella et al. 2021, 2019a, b; Anderson 2016; Le Pelley et al. 2015; Watson et al. 2019). It is an interesting question to what extent an attentional bias for reward may precede addiction problems (e.g., van Hemel-Ruiter et al. 2015), with addiction stimuli becoming instantiations of a general tendency to attend to cues of potential reward.

# 2.2 Attentional Bias Modification (AtBM)

In the last two decades of the twentieth century, hundreds of studies had demonstrated that AtBs were correlated with several mental disorders, mostly in anxiety, both in cross-sectional studies and in longitudinal studies. However, this observation does not prove a causal role of AtB in the etiology or maintenance of the disorder. For this reason, experimental manipulations were developed to (temporarily) change the bias of interest (here AtB), and studies set out to test the effects of these changes on relevant symptoms. Following a first experimental study in which an interpretation bias was experimentally manipulated (Mathews and Mackintosh 2000), Colin

MacLeod, who had decades earlier developed one of the most frequently used assessment tasks for AtB, the dot-probe task (MacLeod et al. 1986), and colleagues published the first study of AtBM (MacLeod et al. 2002). It is important to note that the goal of this study was to test the hypothesized causal role of AtB in anxiety-related symptoms, and not to examine treatment effects. To that end, they invited university students with medium anxiety levels, who were randomized to training to attend toward threat stimuli or to training to attend away from threat. In multiple studies, the authors found that the latter group got less stressed by a subsequent stressful task (solving anagrams), with some evidence indicating that these changes were correlated: those participants who developed the most pronounced attentional avoidance of negative information were the same individuals for whom the AtBM procedure most attenuated the negative emotional impact of the subsequent stress procedure.

Following these early experimental or "proof-of-principle" studies (aimed at establishing causality of the bias in healthy volunteers, Wiers et al. 2018), clinical randomized controlled trials (RCTs) followed. In these, AtBM was used to prevent anxiety when given prior to a major life change that causes stress (See et al. 2009), or as a tool in the treatment of anxiety (Amir et al. 2009; Price et al. 2016). There is, however, still unclarity regarding the efficacy of CBM in this domain (Cristea et al. 2015; Fodor et al. 2020; MacLeod and Grafton 2016), with some arguments for low or no effectiveness also coming back in discussions about the efficacy of CBM in addiction (next section).

In the domain of addiction, first proof-of-principle studies were also conducted with undergraduate student volunteers (Field et al. 2007; Field and Eastwood 2005; Schoenmakers et al. 2007; Wiers et al. 2006). For example, following the "split design" used by MacLeod et al. (2002), see Wiers et al. (2006 for a Figure), Field and Eastwood randomized students to a condition in which they received training to attend to pictures representing alcohol or to a condition where they received training to attend to pictures of non-alcoholic drinks. As in the original study, the manipulation was simple: most or all probes replaced one of the two categories (alcohol in the "attend-alcohol" condition, and non-alcoholic drinks in the "attend non-alcohol" condition). They observed that the attend-alcohol group increased AtB for alcohol, whereas the attend non-alcohol group decreased AtB for alcohol. These effects generalized to other behavior, with an increase for the attend-alcohol group in urge to drink and actual drinking in a taste test. Generalization to untrained pictures was not examined in this study (no untrained pictures were included in the assessment), but was tested in subsequent studies (Field et al. 2007; Schoenmakers et al. 2007). These provided evidence for the conclusion that attentional bias can be successfully manipulated in healthy volunteers, but that the evidence for generalized effects was meager at best (a conclusion that held in later reviews, Wiers et al. 2018).

Given the at least somewhat promising findings of malleability of AtB in hazardous drinkers, a first clinical RCT was performed, in which AUD patients received five sessions of AtBM in addition to their regular (cognitive behavior therapy, CBT) treatment. The AtBM included novel pictures in each training session, to foster generalization (Schoenmakers et al. 2010). Although the study sample was small

(N = 43), significant effects were found on alcohol AtB, including effects on untrained pictures (reduction in the experimental condition, and an increase in a control condition in which patients received irrelevant training using the same stimuli). Note that this increase in alcohol AtB was also found in another study in the absence of training (Cox et al. 2002), and in the control condition of the largest clinical RCT so far, including both AtBM and ApBM (Rinck et al. 2018). Hence, this increase in alcohol AtB appears to be the default development of AtB after detoxification. Another interesting finding, also regarding the still largely open questions about the nature of substance AtB in addiction, was that AtB was successfully changed for the medium-long presentation time (500 ms, large effect size), but no effects were found for early engagement (brief presentation time, 200 ms, Schoenmakers et al. 2010). Finally, promising clinical effects were found; patients in the experimental group had a shorter treatment duration (standard CBT-based therapy; the therapists who judged successful treatment termination were blind to experimental condition), as well as later relapse, compared with patients in the control condition (Schoenmakers et al. 2010). These promising findings are qualified by the small sample size. However, in the largest clinical RCT so far (N = 1.405,Rinck et al. 2018), the AtBM condition also exhibited reduced relapse at 1 year follow-up compared with control conditions (11% less relapse compared with the combined control conditions). While these results in clinical RCTs are promising, one caveat is that dot-probe-based training is often conceived as boring and irrelevant by participants (Beard et al. 2012). As an illustration, in the clinical RCT by Schoenmakers et al. (2010), patients were asked after the training to guess whether they received active or sham training, and almost all patients answered sham training. While this is an encouraging finding from an experimentalist perspective (it is less likely that the effects are based on a placebo effect), it is less desirable from a clinical perspective, and could even lead to an anti-placebo effect (reducing the effectiveness, because of the idea of doing something irrelevant). One could argue that, for clinical applications, one should use placebo effects and avoid anti-placebo effects (Larsen et al. 2021).

In addition to work using a training variety of the dot-probe task, other researchers used a Stroop-based training paradigm as developed by Fadardi and Cox (the alcohol attentional control training program; AACTP, Fadardi and Cox 2009). In this training, participants receive training to systematically avoid (personally relevant) alcohol stimuli, using a series of progressively more difficult tests. Specifically, participants are instructed to respond with a color name, first of the background color of a picture, then of a thin colored line surrounding a bottle, and in the third series the bottles are presented in pairs and the participant is to name the color of the line surrounding the non-alcohol containing bottle. The program also contains psychoeducation about the role of AtB, and the training includes feature-relevant task instructions (e.g., to color-name the line surrounding the non-alcohol containing bottle). This contrasts with dot-probe-based AtBM, where no rationale or feature-relevant instructions are given (participants keep on reacting to the probes following the pairs of stimuli and are not informed that they are systematically trained away from alcohol—although they are likely to notice this at some point).

This difference is important for two reasons. On the one hand, it makes the training more engaging and relevant for participants than dot-probe-based AtBM. On the other hand, the same characteristic also makes it more difficult to create an active control condition and to assess effects of the intervention independent of possible placebo effects.

The first study tested AACTP in hazardous and harmful drinkers (Fadardi and Cox 2009) and found a reduction in drinking and an increase in motivation to change drinking, both in hazardous and harmful drinkers (who reduced their weekly alcohol consumption by some 15% from baseline to follow-up). However, it should be noted that no control condition was included. In a subsequent study, the AACTP was combined with a motivational intervention in a  $2 \times 2$  factorial design in hazardous drinkers (Cox et al. 2015). Compared with the no interventions control group, AACTP led to reduced drinking in the short term, while the motivational intervention led to reductions in the longer term (6 months follow-up), and perhaps surprisingly, the combined intervention did not increase effects. To the best of our knowledge, AACTP has not been tested as an add-on to treatment for AUD. However, it has been tested as an add-on in the treatment of heroin-dependent patients undergoing methodone maintenance therapy (N = 48; Ziaee et al. 2016). The experimental group showed a greater reduction in drug AtB, and in physiological cue reactivity, assessed with blood volume pulse, to indicate changes in sympathetic arousal and in temptation to use in response to drug cues. Effects on relapse were modest (effect on 3 months but not on 6 months follow-up), but low statistical power may have played a role.

In sum, although not many studies tested AtBM as an add-on to clinical treatment of AUD, the two available (dot-probe training) studies found promising effects (Rinck et al. 2018; Schoenmakers et al. 2010) as did an (AACTP) study in opioid-dependent patients (Ziaee et al. 2016). However, a recent study testing add-on effects of gamified AtBM to the treatment of alcohol and cannabis use disorders found no effects (Heitmann et al. 2021). The current state of the evidence is further discussed in Sect. 3.

## 2.3 Approach Bias

In emotion research, a distinction is made between appraisals, which concern a rough first evaluation of a stimulus, and action tendencies, which represent the immediate action readiness component in emotions (Frijda 1986; Frijda et al. 1989, 2014). Motivationally salient stimuli typically elicit an action tendency to either approach or avoid the stimulus. Specifically, approach action tendencies are usually observed for attractive stimuli, and avoidance tendencies for aversive stimuli, with anger being the major exception (negative evaluation combined with approach tendencies, Carver and Harmon-Jones 2009). Given the importance of action tendencies in emotional responses (in addition to appraisals) and the emphasis on attentional bias in the addiction literature, researchers started to assess action

tendencies in relation to addictive behaviors in the first decade of the century. A *manikin* task was developed in which participants move a matchstick figure toward or away from a focal category (e.g., alcohol, Field et al. 2008; e.g., cigarettes, Mogg et al. 2003), with the typical finding that (heavy) substance users are faster to make the manikin approach than to avoid this category, as compared to a control category. Note that this is a so-called relevant feature task with explicit instructions about the relevant feature that participants need to respond to: In one block, they are instructed to approach alcohol (and avoid non-alcohol containing drinks), and in another block reversed contingencies are instructed (avoid alcohol, approach non-alcohol). An approach bias (stronger tendency to approach alcohol) is estimated based on the difference in average RTs in the two blocks.

Another task developed to assess action tendencies is the AAT (approach-avoidance task), going back to the seminal work of Solarz (1960), who first demonstrated that participants are faster to react to positive words with an approach reaction and to negative words with an avoid reaction. Chen and Bargh (1999) developed an approach-avoidance task using a lever, and Rinck and Becker (2007) optimized this in a joystick task. This task includes a zoom feature, so that the size of the stimulus changes upon a response: it increases upon a pull movement (yielding a sensation of approach) and decreases upon a push movement (avoidance). This version was subsequently adapted to an irrelevant-feature task (see Fig. 3) to assess an approach bias for alcohol (Wiers et al. 2009), and other substances (cannabis: Cousijn 2011; cigarettes: Wiers et al. 2013a, b, c), as well as gambling-related stimuli (Boffo et al. 2018). In this irrelevant-feature AAT, participants react with a joystick to a characteristic of the stimulus unrelated to the content, such as format



**Fig. 3** The approach avoidance task (AAT). In the irrelevant-feature version, participants react to the format of the picture (e.g., pull portrait, push landscape pictures). Upon pulling, the picture zooms in, creating a sense of approach; upon pushing, the picture zooms out (shrinks), creating a sense of avoidance. An alcohol-approach bias is assessed when participants are faster to pull than to push alcohol pictures, in comparison with the same difference for a contrast category (e.g., non-alcoholic drinks). In the training versions, alcohol pictures come predominantly in the format that is pulled (approach-alcohol training, only relevant in proof-of-principle studies) or in the format that is pushed (avoid-alcohol training, also clinically relevant)

(e.g., pull pictures in landscape format, push pictures in portrait format, Wiers et al. 2009) or tilt (e.g., pull pictures with a slight left tilt and push pictures with a slight right tilt, Cousijn et al. 2011). Note that it is merely historical coincidence that the manikin task has been primarily used in a relevant feature version, while the AAT task has been primarily used in an irrelevant version, both tasks can be designed either as relevant or irrelevant-feature task (see Field et al. 2011 for a direct comparison).

Notably, cues of addictive behaviors seem to give rise to an automatically activated action tendency in this task (in the sense that participants are faster to approach the addiction-related stimuli than to avoid them, even though they are instructed to react to a feature that is unrelated to the contents of the picture, Boffo et al. 2018; Cousijn et al. 2011; Wiers et al. 2009). This contrasts with general emotion research in which the compatibility effect was found for general positive and negative stimuli with relevant feature or explicit instructions, but not when irrelevant-feature instructions were used (Rotteveel and Phaf 2004). This suggests that the automatic activation of action tendencies may be stronger than for general emotionally relevant stimuli in addictive behaviors or for appetitive stimuli, as an approach bias was also found in G-allele carriers of the OPRM1 gene, but not for general positive and negative stimuli (Wiers et al. 2009). This allelic variation has also been associated with cue-induced craving (e.g., Van Den Wildenberg et al. 2007) and with increased neural cue reactivity to substance cues (Bach et al. 2015; Filbey et al. 2008; Korucuoglu et al. 2017).

An advantage of the irrelevant-feature instructions in this assessment task (the irrelevant-feature AAT) is that it can be easily changed to a bias modification instrument without changing the instructions, similar to dot-probe-based AtBM (Wiers et al. 2010). However, this comes with a cost, as the reliability (internal consistency) of irrelevant-feature tasks is lower than that of relevant feature tasks (Field et al. 2011). With both types of tasks, heavy substance users (and gamblers) have been found to have an approach bias, which is typically not found in non-users or light users (review: Kakoschke et al. 2019). It should be noted that these findings indicate group differences, but that there is a substantial minority of AUD patients who do not demonstrate an approach bias for alcohol, but rather an avoidance bias (e.g., Piercy et al. 2021).

Although in the original AAT, a joystick was used, AATs with response keys have also been used, which might take away part of the embodied nature of the response, but still yielded effects in some studies (e.g., Peeters et al. 2012). A recent study in the domain of problematic porn use directly compared assessment with a joystick and a keyboard. It found better results for the joystick (Kahveci et al. 2020), which is therefore still recommended (but may become harder to obtain over time). For this reason, researchers are testing mobile versions, which include arm movements using a phone or tablet (Boendermaker et al. 2015a; Zech et al. 2020) and a VR version where the (avatar) body moves toward the stimulus (Rougier et al. 2018). Note that also an approach-avoid version of the implicit association task (IAT) has been developed, in which four categories of words (two pairs: approach or avoid and alcohol or non-alcohol) are sorted using two response keys (Ostafin and

Palfai 2006). In one sorting condition, participants use the same response key for alcohol words and approach words (and the other key for non-alcohol words and avoid words). In the other sorting condition, alcohol words require the same response as avoid words (and non-alcohol words as approach words). The IAT effect concerns the difference in RTs (and errors) between these two sorting conditions (Greenwald et al. 2003, 2021). When participants are faster to sort alcohol with approach words, this is interpreted as a relatively stronger memory association between alcohol and approach tendencies, compared with alcohol and avoid tendencies (assuming that the effect is more driven by alcoholic than non-alcoholic drinks). Note that there is some controversy concerning the exact interpretation (construct validity) of IAT scores (De Houwer et al. 2005, 2020; Greenwald et al. 2009; Rothermund and Wentura 2004), but it is clear that the IAT is a reliable measure, much more reliable than irrelevant-feature measures (De Houwer and De Bruycker 2007; Greenwald et al. 2021; Roefs et al. 2011).

### 2.4 Approach Bias Modification (ApBM)

Following the same logic of AtBM, the assessment alcohol AAT (Wiers et al. 2009), was transformed into a task aimed at modifying the approach bias, in a first proof-ofprinciple study in hazardously drinking students (Wiers et al. 2010). Specifically, students were randomly assigned to an approach-alcohol condition or an avoidalcohol condition (split design as in MacLeod et al. 2002; Field and Eastwood 2005). In both conditions, the AAT started with the usual irrelevant-feature assessment task. Participants were instructed to respond with a pull movement to one type of pictures (e.g., landscape) and with a push movement to the other type of pictures (e.g., portrait). These responses were first practiced using gray rectangles, followed by pictures of alcohol and non-alcohol drinks, of which half were pulled and half pushed of both types. Then, without notification or change in instruction, the task transformed into a training task, where alcohol pictures were consistently pulled, and non-alcohol pictures pushed (approach-alcohol condition) or alcohol pictures were consistently pushed and non-alcoholic drinks pulled (avoid-alcohol condition). This manipulation resulted in a generalized change in approach bias on the AAT both for trained and for untrained pictures, so that participants in the approach-alcohol condition became faster in pulling alcohol (and pushing non-alcoholic drinks) and participants in the avoid-alcohol condition became faster in pushing alcohol (and pulling non-alcoholic drinks). Interestingly, an effect was also found on the approach-avoid IAT using words (which is a strong generalization, as participants were trained with a training version of the joystick AAT using pictures). Moreover, in participants who were successfully trained, an effect was found in a subsequent taste test, where heavy drinkers who had been successfully trained to avoid alcohol drank less beer than heavy drinkers who had been successfully trained to approach alcohol (no difference was found in light drinkers). Note that these generalized effects were unexpected, as they had not been found after a single session of AtBM in healthy volunteers (Field et al. 2007; Schoenmakers et al. 2007).

Given these promising findings in a first proof-of-principle study, ApBM was tested as an add-on to regular treatment in a first large clinical RCT (N = 214, Wiers et al. 2011). Two experimental conditions were included, both consisting of four sessions of ApBM in which participants were consistently trained (four sessions including 200 trials each) to respond with a push response to alcohol pictures and with a pull response to non-alcohol pictures. The one difference between the two experimental conditions was that one used an irrelevant-feature version (as in the proof-of-principle study described above: instructions remained the same, but now alcohol was consistently pushed away), while patients in the other condition were explicitly instructed to push away alcohol pictures and to pull non-alcohol pictures. Given that the crucial procedural details (contingencies) did not differ between these groups, nor did they differ in any of the outcome measures, they were combined into one active ApBM group, as were the two control conditions which included either only a continued assessment task (equally often pushing and pulling both alcohol and non-alcohol pictures) or no training at all. As in the proof-of-principle study, generalized effects were found on untrained pictures in the AAT assessment task and on the verbal IAT (strong generalization). While patients were faster (on average) to sort alcohol with approach words before training (alcohol-approach association dominated), this changed to faster sorting of alcohol with avoid words in the active ApBM group, while no change was observed in the control group. The most striking result came at the one-year follow-up, where it was found that patients in the experimental conditions had a 13% lower chance of relapse 1 year after treatment discharge (46% vs. 59%). Of note, the reduced relapse rate was not mediated by the change in alcohol-approach tendencies, as assessed either with the AAT or with the IAT. However, a subsequent more fine-grained analysis into components of the IAT suggested that an increased avoidance bias for alcohol stimuli partly mediated the improved clinical outcomes (Gladwin et al. 2015). This pattern is congruent with the rationale of ApBM, but is at odds with another study which reported that a stronger AAT tendency to avoid alcohol during treatment was predictive of relapse (Spruyt et al. 2013; see Wiers et al. 2013c; De Houwer et al. 2020, for possible explanations). In short, this relates to an alternative interpretation of automatic processes in addiction, discussed later in ABC training, focusing on automatic inferences. From this interpretation, some people may interpret the task as what they desire (to not be attracted by alcohol anymore), while others react on what the substance invokes in them (a desire to approach). This could be related to the distinction between first- and second-order desires (desires what you desire, here, not to desire alcohol anymore) in philosophy (Frankfurt 1971).

In a series of subsequent studies, the results of reduced relapse rates caused by ApBM were replicated. First, in a replication study including 509 patients (Eberl et al. 2013), participants were either trained to avoid alcohol during 12 sessions, or they received no training (as the first study found no difference between an active and this passive control condition) as an add-on to their (CBT-based) inpatient treatment. Patients in the active training condition were found to have 9% less

chance to have relapsed 1 year later compared to the (passive) control condition. In this study, both mediation and moderation were observed, with the change in alcohol-approach tendency (assessed with the AAT) mediating the clinical outcome, and the strength of the alcohol-approach bias at pretest predicting stronger change in bias.

In subsequent analyses, the optimal number of sessions was investigated, including predictors of the number of sessions needed (defined as the point where the learning curve became flat, Eberl et al. 2014). The mean number of sessions was six, but there was large variability, with some patients needing only two sessions and others still improving in the 12th session (note that learning can take even longer in AUD patients with Korsakov syndrome, Loijen et al. 2018). Disappointingly, none of the baseline variables predicted individual differences in the learning rate.

Second, the largest CBM RCT so far combined ApBM and AtBM (Rinck et al. 2018) as an add-on to the treatment of AUD. Specifically, 1,405 AUD patients were randomized over 7 conditions: 3 active CBM conditions, which consisted of 6 sessions of ApBM, 6 sessions of AtBM, or 3 of each; compared to 3 matched control conditions (same setup without a training contingency, hence prolonged assessment); and a no training control condition. Participants in all three CBM conditions exhibited less relapse compared with the control conditions (8.4% on average). Mediation and moderation effects were not replicated, but it should be noted that many data were missing for the bias measures, as the study took place during regular treatment.

Third, the most recent of this series of studies in the same clinic (Salemink et al. 2021) assessed effects of ApBM in 729 AUD patients, of whom 20% also had an internalizing disorder (anxiety or depression). Patients received either 12 sessions of ApBM or no training as an add-on to treatment (as in Eberl et al. 2013, note that these are unique patients, not overlapping with those of the Eberl et al. 2013, analyses). In this study, adding ApBM to treatment led to 10% less relapse a year after treatment discharge. Interestingly, results were better for patients who had a comorbid internalizing disorder, compared with the AUD-only patients.

All of these studies took place in the same clinic, with the same core team of researchers. Therefore, an important question is whether the results would replicate in a different setting. In another series of studies, Manning and colleagues tested effects of ApBM in Australia, where the setting was different; it was used as an add-on during detoxification. In a first study, 83 participants were randomized to ApBM or sham training during the detox period (Manning et al. 2016). Primary outcome variable was continuous abstinence during the 2 weeks after detox. Abstinence was higher in the ApBM condition: at statistical trend level in the intention-to-treat analysis, and significantly in the per-protocol analysis (including only patients who performed all four sessions of training). In a recent larger replication multicenter RCT (Manning et al. 2021), 300 patients were randomized to receive either ApBM or sham training. Patients receiving ApBM were 12% less likely to have relapsed during the 2 weeks follow-up. In the per-protocol analysis, this was 17%. In a follow-up study of the same sample with outcomes after 3, 6, 9, and 12 months, the difference was still significant after 3 months but not anymore after, although the

absolute difference was still 7% less relapse after 12 months in people who had received the training (Manning et al. 2022).

In summary, in two series of RCTs across different settings, ApBM has been found to consistently improve treatment outcomes, with 7 to 17% reductions in relapse 1 year after treatment discharge, which has led to the inclusion of this type of CBM as an advised add-on to the clinical treatment of AUD in the countries where these trials took place (Germany and Australia; see introduction). However, it should be mentioned that there is one (as-yet unpublished) recent RCT we are aware of, which did not find an add-on effect of CBM in the treatment of AUD (in Belgium, Spruyt et al. unpublished data); see Table 1. Note that the latter study may have been underpowered for replicating the small effects that were found earlier, especially when evaluating a binary outcome (relapse or not). Note further that there are other studies on effects of CBM in AUD patients, but these were not primarily powered for clinical outcomes (but for example for neural effects of training: Wiers et al. 2015a, discussed in the next section), and studies that explored the combined effects of CBM with neurostimulation (den Uyl et al. 2017, 2018; Dubuson et al. 2021, discussed in Sect. 5).

Further, although effects of ApBM as add-on to the treatment of AUD have been almost exclusively positive, it does not imply that ApBM is a magic bullet against all alcohol problems. For instance, it was not found to be effective as stand-alone intervention for problem drinkers administered over the web (Van Deursen 2019; Wiers et al. 2015a, b, c). In both studies, problem drinkers successfully decreased drinking, both in the CBM conditions and in the placebo-control conditions (non-specific time effect), which is the general conclusion concerning the effectiveness of CBM in heavy or problem drinkers over the web (Jones et al. 2018; Van Deursen 2019; Wiers et al. 2015a, b, c). In addition, in a study with hazardously drinking students not motivated to change, ApBM did not yield effects (Lindgren et al. 2015). In sum, it seems that in studies where ApBM was added to abstinenceoriented treatment for patients motivated to change their drinking behavior, ApBM has almost consistently shown to have beneficial effects. However, when participants only want to reduce their drinking or are not motivated to change their drinking, no differential effects are found in comparison with an active control condition (in volunteers who want to reduce drinking, reduced drinking is found across conditions, and in volunteers who participate for other reasons, typically only short-lived effects are found in case the bias is successfully changed, or no effects on drinking behavior are found; see Wiers et al. 2018 for a review).

ApBM has also been tested for other addictive behaviors, mostly for cigarette smoking (Kong et al. 2015; Machulska et al. 2016; Wen et al. 2020; Wittekind et al. 2019b). As in the alcohol studies, some studies were web-based only, and these did not find (differential) effects (Wen et al. 2020; Wittekind et al. 2019a). Yet, most similar to the conditions where an almost consistent effect has been found as an add-on to the abstinence-oriented treatment of AUD is a study where ApBM was also added to a well-established smoking cessation program (Wittekind et al. 2019b), and this study also found no effects. Before we conclude that ApBM does not work for smoking, it may be good to point to two preclinical studies that modified the

Table 1 CBM as add-on to the clinical treatment of AUD

group/training Sessions/ Follow- (n) IAT-based 5 sessions/ 3- sham (22) 3 weeks month Sham or no 4 sessions/ 1-year training + TAU (106) No training + 12 ses- TAU (227) sions/6 weeks Alc control + 8 sessions/ 1- SA AtBM 4 weeks month (24) Alc control + SA debM 4 weeks month (24) Alc control + SA control - SA control			Experimental	Control			Outcomes		
(a) (n) (n) time (b) time (c) (d) (d) time (d) (e) (d) (e) (d) (d) (e) (d) (e) (d) (e) (d) (e) (d) (e) (e) (e) (e) (e) (e) (e) (e) (e) (e		Sample	group/training		Sessions/	Follow-			
AUD         AtBM + TAU         IAT-based         5 sessions/         3-           (43)         (21)         sham (22)         3 weeks         month           AUD         ApBM +         Sham or no         4 sessions/         1-year           (475)         TAU (108)         TAU (106)         1-year           AUD         ApBM +         No training +         12 ses-         1-year           AUD         ApBM +         Alc control +         8 sessions/         1-           AUD         Ac AtBM +         Alc control +         8 sessions/         1-           AUD         Ac AtBM +         Alc control +         8 sessions/         1-           AUD         AAT + detox -         Sham +         4 weeks         month           AUD         AAT + detox -         Sham +         4 days         2-week           AUD         ApBM +         Sham + TAU         6 sessions   1-year           AUD         ApBM +         Sham + TAU         6 sessions   1-year           AUD         ApBM +         Sham + TAU         6 sessions   1-year		(n)	(n)	(n)	time	dn	Abstinence/drinking	Task (s)	Remarks
AUD         ApBM +         Sham or no         4 sessions/         1-year           AUD         ApBM +         Sham or no         4 sessions/         1-year           (214)         TAU (108)         training +         12 ses-         1-year           AUD         ApBM +         No training +         12 ses-         1-year           (475)         TAU (248)         TAU (227)         sions/6         1-           AUD         SA control         SA AtBM         4 weeks         month           (86)         (20)         (24)         4 weeks         month           AUD         AAT + detox-         Sham +         4 sessions/         2-week           AUD         AAT + detox-         Sham +         4 days         3-weeks           AUD         AAT + detox-         Sham +         4 days         1-year           AUD         ApBM +         Sham + TAU         6 sessions         1-year           AUD         ApBM +         Sham + TAU         6 sessions         1-year		AUD	AtBM + TAU	IAT-based	5 sessions/		RR: ×	VPT	EG: relapse 1 month later
AUD         ApBM + TAU (108)         Sham or no training + TAU (106)         1-year training + TAU (106)           AUD         ApBM + TAU (227)         No training + 12 ses-sions/6         1-year sions/6           AUD         ApBM + Alc control + Sessions/7         SA AtBM         4 weeks month           AUD         SA control SA AtBM + Alc control + SA AtBM + Alc control + SA AtBM SA control (20)         SA control (24)         24)           AUD         AAT + detox - Sham + Alc control + SA AtBM SA control (20)         SA control (20)         200           AUD         AAT + detox - Sham + Alc control (41)         4 weeks month (42)           AUD         ABBM + SA Control (20)         200           AUD         ABBM + Sham + TAU (44)         4 days           AUD         ABBM + Sham + TAU (5 sessions (1,405)         1-year (1,405)		(43)	(21)	sham (22)	3 weeks	month		EG: AtB↓ CG: ×	and treatment discharge 1 month earlier
AUD ApBM + Alc control + 8 sessions/ AUD AAtBM + Alc control + 8 sessions/ AUD SA control   SA AtBM   Alc control + 8 sessions/ AUD SA AtBM + Alc control + 8 sessions/ AUD AAT + detox - Sham + A sessions/ AUD AAT + detox - Sham + A sessions/ (83) ification (41) detoxification   4 days   AUD ApBM + Sham + TAU   6 sessions   1-year   (1,405) TAU (238)   316   316   316   (475) TAU (248)   TAU (248)   (476) TAU (248)   TAU (248)   (476) TAU (248)   TAU (248)   (476) TAU (248)   TAU (248)   (477) TAU (248)   TAU (248)   (475) TAU (248)   TAU (248)   (476) TAU (248)   TAU (248)   (476) TAU (248)   TAU (248)   (477) TAU (248)   TAU (248)   (478) TAU (248)   TAU (248)   (475) TAU (248)   TAU (248)   (476) TAU (248)   TAU (248)   (477) TAU (248)   TAU (248)   (478) TAU (248)   TAU (248)   (478) TAU (248)   TAU (248)   (478) TAU (248)   TAU (248)   (479) TAU (248)   TAU (248)   (470) TAU (248)   TAU (2		AUD	ApBM +	Sham or no	4 sessions/	1-year	RR:	AAT:	Effects generalized to
AUD ApBM+ No training + 12 ses- 1-year (475) TAU (248) TAU (227) sions/6 weeks  SA and Alc AtBM + Alc control + 8 sessions/ 1- AUD SA control (24) Alc control + 3 sessions/ 1- SA AtBM Alc control + 3 sessions/ 1- SA AtBM Alc control + 3 sessions/ (20) AUD AAT + detox - Sham + 4 sessions/ (20) AUD AAT + detox - Sham + 4 days  AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)		(214)	IAU (100)	TAU (106)			EG 40% < CG 39%	AApp. EG	unuamed sumun (AA1) and verbal IAT
AUD ApBM+ No training + 12 ses- 1-year (475) TAU (248) TAU (227) sions/6 weeks  SA and Alc AtBM + Alc control + 8 sessions/ 1- AUD SA control SA AtBM 4 weeks month (86) (20) Alc AtBM + Alc control + 8 sessions/ 1- AUD Act AtBM SA control (24) AUD AAT + detox Sham + 4 sessions/ 2-week (83) ification (41) detoxification 4 days  AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)								CG	
AUD         ApBM + (475)         No training + 12 ses- (1-year (475)         1-year (475)           AL         TAU (227)         sions/6 (20)         1- weeks           SA and Alc AtBM + AUD SA control (86)         SA AtBM (24)         4 weeks month (40)           AUD AAT + detox - (22)         AC control (20)         24)           AUD AAT + detox - (83)         Sham + (42)         2-week (42)           AUD ABM + (316)         Sham + TAU (5 sessions (1-year (1405) (1405) (1405) (316)         1-year (1405) (316)								IAT: $\triangle ApB$ : EG > CG	
AUD   APD   APD   APD   Sions/6	t al.	AUD	ApBM +	No training +	12 ses-	1-year	RR:	AAT: EG:	Change in AAT partially
SA and		(475)	TAU (248)	TAU (227)	sions/6		EG 48.8% <	ApB→AvB	mediated training effect on
SA and	T			,	weeks	1	CG 37.3%	× :5	relapse rate
AUD   SA control   SA AtBM   4 weeks   month     (86)	ı et al.	SA and	Alc AtBM +	Alc control +	8 sessions/	<u>-</u>	FU: ×	VPT: ×	Significant or trending
(86) (20) (24) Alc AtBM + Alc control + SA AtBM   SA control   (22) (20) AUD   AAT + detox - Sham + 4 sessions/ 2-week (83) ification (41)   detoxification   4 days   (42) (42) AUD   ApBM + Sham + TAU   6 sessions   1-year   (1,405)   TAU (238)   316		AUD	SA control	SA AtBM	4 weeks	month			decreased in all attention
Alc AtBM + Alc control + SA AtBM   SA control    (22) (20)  AUD		(98)	(20)	(24)					trial-level bias score param-
SA AtBM   SA control   (22)			Alc AtBM +	Alc control +					eters (but not traditional
AUD AAT + detox- Sham + 4 sessions/ 2-week (83) ification (41) detoxification 4 days (42) (42)  AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)			SA AtBM (22)	SA control (20)					attention bias scores)
(83) ification (41) detoxification 4 days (42)  AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)		AUD	AAT + detox-	Sham +	4 sessions/		RR:		At the 2-week follow-up,
AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)		(83)	ification (41)		4 days		EG 31.4%. < CG		participants reported a
AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)				(42)			52.8%		higher rate of abstinence in
AUD ApBM + Sham + TAU 6 sessions 1-year (1,405) TAU (238) (316)									ure Controls
(1,405) TAU (238) (316)		AUD	ApBM +	+ TAU		1-year	RR:	VPT: AAtB:	Merged control groups
		(1,405)	TAU (238)	(316)			AtBM 44.8% <	EG < CG	(sham training and no train-
No training + TAU (366)			AtBM + TAU (230)	No training + TAU (366)			ApBM 47.9% <	AAT:	ing) for analyses

Heitmann et al.   AUD or   ABM + TAU   Sham + TAU   7 weeks   1-year   RR × (2021)   (169)   AUD   ApBM + Sham + TAU   4 sessions/ 2   RR	combime 48.6% <   CG 55.6%	o < AApB: EG > CG	
al. AUD ApBM+ Sham + TAU 4 sessions/ 2  al. AUD ApBM+ No-training + 12 ses- 1-year  (729) TAU (304) TAU (425) sions/4  AUD ApBM + SI + ApBM + 6 sessions/ 1-year  (434) TAU (214) sham SI+ 2 weeks  d (155 at (49) VPT Sham AAT + 8 sessions 3 follow-up) VPT (43) sham AAT + 8 sessions (29)  AUD Standard Sham + TAU 6 sessions/ 3- 10w-up) VPT (43) sham AAT + 8 sessions (34)  AUD Standard Sham + TAU 6 sessions/ 3- 10w-up) (242) Alc-IT + TAU (79) 2 weeks month (84)	1-year	000T (AtB): ×	No significant differences between conditions
al. AUD ApBM+ No-training + 12 ses- 1-year (729) TAU (304) TAU (425) sions/4 sions/4 Add TAU (214) Sham SI+ 2 weeks 1-year (434) TAU (214) Sham SI+ 2 weeks 1-year Add (155 at (49) VPT Sham AAT + 8 sessions 3 follow-up) VPT (43) sham AAT + 8 sessions 3 follow-up) VPT (44) sham AAT + 8 sessions 3 follow-up) VPT (45) sham AAT + 8 sessions 3 follow-up) VPT (45) sham AAT + 8 sessions 3 follow-up) VPT (45) sham AAT + 8 sessions 3 follow-up) VPT (45) sham AAT + 8 sessions 3 follow-up) VPT (45) sham AAT + 8 sessions 3 follow-up) VPT (45) sham AAT + 8 s	2 weeks	1.9%	For those training-session > 4, EG-RR < CG-RR by 17.0%
al. AUD ApBM + SI + ApBM + 6 sessions/ 1-year (434) TAU (214) sham SI+ 2 weeks TAU (220)  AUD AAT + VPT Sham AAT + 8 sessions 3 follow- 1st follow-up) VPT (43) sham AAT + 8 sessions 3 follow-up) VPT (43) sham AAT + 8 sessions 3 follow- 1st follow-up) VPT (43) sham AAT + 8 sessions 3 follow- 1st follow-up) Standard Sham AAT + 8 sessions/ 34 (34) sham VPT (34) sham	1-year	1 %0	TS: no relapse or relapse shorter than 3 days within 4 weeks after treatment
d (155 at (49) VPT Sham AAT + 8 sessions 3 follow-1st follow-up) VPT (43) Sham AAT + 8 ham (29) ups low-up) VPT (43) Sham AAT + 8 ham VPT (34) Sham AAT + 8 ham VPT (34) Sham AAT + (242) Alc-IT + TAU (79) 2 weeks month (84)	1-year	AAT: ×	SI + ApBM: evaluation of nonalcoholic beverage↑ TAU included ApBM
AUD Standard Sham + TAU 6 sessions/ 3- (242) Alc-IT + TAU (79) 2 weeks month (84) Improved		× AAT: × VPT: ×	No effects on relapse.
ARC-11 + 1AC (79)		GNG (Alc-IT alcohol related error rate 1)	Standard Alc-IT (Go/Nogo = 50/50) Improved Alc-IT (Go/Nogo = 75/25) Alc-IT might be a promising add-on

modification, ApB approach bias, AvB avoidance bias, SA social anxiety, tDCS transcranial direct current stimulation, Alc-IT alcohol-specific inhibition training, RR relapse rate;:  $\times$  = intervention showed no effect on outcome;  $\uparrow$  = increase;  $\downarrow$  = decrease; AC alcohol consumption, AD abstinent days, HD heavy drinking days, SI selective inhibition training, VPT Visual Probe Task, TS treatment success, OOOT Odd-One-Out assessment task, FU follow-up

procedure and found more positive effects through personalization of alternatives (Kopetz et al. 2017; Wen et al. 2021), which may be helpful because unlike ApBM in alcohol, where the alternative category is meaningful (non-alcohol containing drinks), this is not the case in standard ApBM for cigarette smoking, where visually matched alternatives are typically used such as someone holding a pen rather than a cigarette. These alternatives and the related new ABC training are discussed in Sect. 6.

Finally, while AtBM was developed in the context of anxiety disorders (MacLeod et al. 2002) and later "translated" to the field of addictions (Field et al. 2007; Schoenmakers et al. 2007, 2010), ApBM was developed in the field of addiction<sup>2</sup> (Wiers et al. 2010, 2011), and later also applied to anxiety (Amir et al. 2013) and depression, by Becker and colleagues (2019) and Vrijsen et al. (2018), with promising findings. Note that in these instances, it is primarily an approach (rather than an avoidance) reaction that is trained, toward a feared object (anxiety) or toward positive stimuli (depression).

### 2.5 (Evaluative) Memory Bias

The third cognitive bias often reported in addictions concerns a memory bias. Different types of measures have been used, open-ended measures, where participants write down (or say) the first association that comes to mind (Stacy et al. 1994, 2006; Stacy 1997), where different stimuli are used, such as ambiguous words (e.g., first association to "draft"), or first behavior that comes to mind to a situation (e.g., Friday night, feeling good). Note that even earlier, a measure including multiple associations to a stimulus was developed (Szalay et al. 1992). These measures are good predictors of (prospective) addictive behaviors (reviews: Stacy et al. 2006; Stacy and Wiers 2010), and are also reliable (Shono et al. 2016). The second class of measures is reaction time-based. Most researchers use varieties of the IAT, which can be flexibly used to assess relative ease of sorting alcohol (as compared with non-alcoholic drinks) together with valence (Houben and Wiers 2008; often referred to as "implicit attitudes," e.g., Wiers et al. 2002), or with different attributes, like arousal (Houben and Wiers 2006; Wiers et al. 2002). The aforementioned approachavoid dimension (Ostafin and Palfai 2006), and more recently, drinking-identity associations have been studied intensively (e.g., Lindgren et al. 2012, 2016). Other measures have also been used, especially to assess implicit attitudes, including the Extrinsic Affective Simon Task (e.g., de Jong et al. 2007), and the Affect Misattribution Procedure (Payne et al. 2005, 2016). The dominant interpretation of these findings is that the more readily participants can associate a positive attribute

<sup>&</sup>lt;sup>2</sup>Note that there is an earlier study on ApBM in the field of social cognition (Kawakami et al. 2007), but we developed the training independently; based on AtBM, the first data were collected in 2005, but publication took a while (as is often the case with new interventions).

with alcohol (or other substances), the more they drink. These attributes can be expected outcomes (e.g., combinations of positive and arousing expectancies, like fun), but also general positive or negative stimuli can be used (see Houben et al. 2010b for a direct comparison). Finally, it should be reiterated that there is discussion regarding the exact interpretation of the reaction time (RT) measures, especially regarding the IAT (De Houwer et al. 2005, 2020; Rothermund and Wentura 2004).

### 2.6 Evaluative Memory Bias Modification

In AtBM and ApBM, modification is typically performed with a training variant of a measurement instrument (e.g., dot-probe, alcohol-Stroop, or AAT), where a contingency is built into the task to change the bias (e.g., avoid alcohol). This is not the case in attempts to change biases in evaluative memory, where different procedures have been used, notably evaluative conditioning (EC) and selective inhibition.

In EC, a stimulus is consistently paired with a category of valenced stimuli (e.g., always when there is an alcohol picture, there is also a negative picture, e.g., Houben et al. 2010c). To the best of our knowledge, EC has not been used as an add-on in the treatment of AUD<sup>3</sup>; for that reason we only describe this method briefly here. Several proof-of-principle studies in heavy drinking volunteers have shown promising effects (Houben et al. 2010a, c; Noel et al. 2019; Tello et al. 2018; Zerhouni et al. 2019), which could stimulate researchers to test the procedure in AUD patients. Regarding the moderators of EC effects, there is growing evidence that conscious awareness of the evaluative stimuli is needed for EC effects to occur (Corneille and Stahl 2018; De Houwer et al. 2020; Hofmann et al. 2010; Sweldens et al. 2014); see also Sect. 4 below.

A second method used to change alcohol evaluations is selective inhibition. In this procedure, a specific category of stimuli is systematically followed by an inhibitory response (Chen et al. 2016; Veling et al. 2008, 2017). Typically, a Go/NoGo task is used, where, in the active condition, the focal category (e.g., alcohol) is always paired with a NoGo signal (Houben et al. 2010a, 2012). In both studies, healthy volunteers (hazardously drinking students) in the active condition showed reduced alcohol consumption in the short term (one-week follow-up). Both studies also showed effects on the evaluation of alcohol (which became more negative in the active condition), and in the second study, no effect was found on a general inhibition task (Stop task), in line with the idea that the effect of selective inhibition is achieved through stimulus devaluation and not through a general effect on inhibition (see also Fig. 1).

Selective inhibition has been successfully used across several health domains as a preventive intervention, as a first meta-analysis showed (Allom et al. 2015), but there

<sup>&</sup>lt;sup>3</sup>One could argue that ApBM is a form of EC, as in ApBM negative *responses* are consistently paired to addiction-relevant cues.

are no published studies yet testing selective inhibition as an add-on to the treatment of AUD (one feasibility study with self-identified people with AUD online, Strickland et al. 2019). However, there are two recent studies, in which selective inhibition has been added to the treatment of AUD (one just accepted and one still under review). The first took place in the Salus Clinic Lindow, where ApBM has become part of regular treatment after consistent positive add-on effects after four large RCTs (Eberl et al. 2013; Rinck et al. 2018; Salemink et al. 2021; Wiers et al. 2011). Against this background, selective inhibition was added as extra add-on, first in the standard version as used in preclinical studies (Houben et al. 2011a, 2012), in which in the active training condition, based on the Go/NoGo task, participants always react with a NoGo response to alcohol-related stimuli. In the control condition, there is no contingency (a Go or NoGo response is paired equally often with alcohol as with non-alcohol). No extra add-on effect was found in this context, which could mean either that it does not add to ApBM which was already part of the treatment or that this specific training has no add-on effect. Regarding the specific inhibition training, it should be noted that in the most frequently used training variety of the GoNoGo task, the inhibited category (e.g., alcohol) appears in half of the trials, while basic research has shown that the inhibition effect is optimal when the inhibited category is more rare (typically 25% is used), and there are indications that this may also yield the largest effect on evaluation (Chen et al. 2016).

In the second RCT in which selective inhibition was added to the treatment of AUD (Stein et al. 2022), both the "standard" selective inhibition condition (with 50% alcohol pictures, always triggering a NoGo reaction) and a version in which alcohol stimuli were rare (25% of the trials) and were always combined with an inhibitory response, along with a control condition (as in standard selective inhibition studies, 50% alcohol stimuli, half of the time requiring an inhibitory response, protocol: Tschuemperlin et al. 2019). While standard selective inhibition training yielded no effect, improved inhibition training with relatively rare alcohol stimuli did improve outcomes at 3 months follow-up (Stein et al. 2022). These findings indicate that optimized selective inhibition training could also be a valuable add-on training in the treatment of AUD. As such, promising findings have been found for use as add-on training in the treatment of AUD for all three frequently used forms of CBM: AtBM, ApBM, and selective inhibition.

# 3 Cognitive Bias Modification as Add-On in the Treatment of AUD: Update of the Evidence

Thus far, there have been two meta-analyses regarding effects of CBM in addiction. The first combined proof-of-principle (PoP) studies in healthy volunteers with clinical RCTs in AUD patients (Cristea et al. 2016). It concluded that CBM was effective in changing the targeted cognitive bias, but did not have a significant effect on clinical outcomes, and that therefore the clinical utility of CBM for addiction was

"seriously doubted." However, this meta-analysis was criticized for combining these two types of studies (Wiers et al. 2018; see also the commentaries following the original publication in PlosOne), although they represent different stages of the experimental medicine approach to intervention development (Sheeran et al. 2017): While PoP studies are aimed at testing the causal status of a construct (e.g., cognitive bias) in relation to the problem behavior (e.g., excessive drinking), clinical RCTs are aimed at testing efficacy of the intervention in patients, and both study types should therefore not be combined into a single analysis. In PoP studies, healthy volunteers are recruited and often randomized to a condition in which the bias is temporarily *increased*, in order to study whether this leads to a temporary increase in the problem behavior (e.g., Field and Eastwood 2005; MacLeod et al. 2002; Wiers et al. 2010). Obviously, this is not done in clinical RCTs with patients (for detailed discussions regarding the different phases of the experimental medicine approach to intervention development, see Sheeran et al. 2017; Wiers et al. 2018). Importantly, participants in the large majority of included studies were healthy volunteers in PoP studies, who took part in the included studies for extrinsic motivators such as course credit or money and not because of a motivation to change their drinking (Wiers et al. 2018). Hence, the conclusion that the clinical effects of CBM were seriously doubted was based on an analysis that included primarily PoP studies in healthy volunteers, while the included clinical RCTs all found clinically relevant effects (later relapse or reduced relapse rates at one-year follow-up).

Subsequently, a first meta-analysis was done including clinical RCTs only, where an inclusion criterion was that participants were motivated to change their addictive behavior and were told that the goal of the intervention was to help them reduce their substance use (Boffo et al. 2019). In this Bayesian meta-analysis of individual participant data, 14 studies were included (all on AUD or smoking, as in Cristea et al. 2016). Small but significant effects were found on cognitive bias and, on relapse rates, no effect on substance use. The latter appears to primarily resonate the findings of Internet trials, in which participants choose their own goal, and most choose to reduce use, which they successfully do, whether they are in the active CBM condition or in an active control (sham training) condition (e.g., Wiers et al. 2015a, b, c). This meta-analysis included four studies in which a variety of CBM was added to the treatment of AUD, which have been summarized in the previous section, one assessing add-on effects of AtBM (Schoenmakers et al. 2010), and three assessing add-on effects of ApBM (Eberl et al. 2013; Wiers et al. 2011, 2015b). In addition, it included several studies in which community samples of heavy or problem drinkers received training, as a stand-alone intervention (Clerkin et al. 2016; Cox et al. 2015; Wiers et al. 2015a, b, c). While the studies of the first type found positive clinical outcomes (later or reduced relapse, only not significant in the small study focusing on neurocognitive outcomes, which will be discussed in the next paragraph, Wiers et al. 2015a, b, c), studies of the second type generally found no differential effects on alcohol use compared with the (active) control condition. There are two likely explanations for this difference, either CBM works only as add-on to clinical treatment, or only when participants have an abstinence goal, or both. This cannot be determined now, as these variables are highly correlated: abstinence was the treatment goal in almost all clinical studies where CBM was added to treatment as usual, and was hardly ever the goal in the studies in which problem drinking volunteers participated.

Table 1 summarizes the clinical RCTs where CBM was added to clinical treatment of AUD, Table 2 summarizes other RCTs in which CBM was used to reduce problem drinking in non-clinical settings, and studies in AUD patients which had a different purpose than clinical effects (e.g., study neural effects of CBM in a small sample). We repeated the search as described in Boffo et al. (2019), and for this chapter included all studies on CBM effects in relation to alcohol use disorders.

Regarding the studies that primarily tested clinical outcomes of adding a variety of CBM to treatment of AUD, the large majority found positive effects, but these effects are rather small (around 10% less relapse at one-year follow-up, which would yield a number needed to treat (NNT) of 10, which is similar to the small effect sizes of medication for AUD (Jonas et al. 2014). There are also some negative findings (no add-on effect), which could be related to the type of CBM used (e.g., gamified rather than standard CBM, Heitmann et al. 2021), and or treatment goal (positive findings have primarily been found in inpatient settings with an abstinence goal (Eberl et al. 2013; Manning et al. 2016, 2021; Rinck et al. 2018; Salemink et al. 2021; Schoenmakers et al. 2010; Stein et al. 2022; Wiers et al. 2011), with some exceptions (Clerkin et al. 2016, an underpowered study, N = 86 with four conditions; and the as-yet unpublished study by Spruyt et al. unpublished data; note that in Heitmann et al. some patients had an abstinence goal and others not, and both AUD and CUD were treated).

The studies in Table 2 can be grouped into two categories. The first concerns web-based studies where varieties of CBM have been tested as stand-alone interventions for self-identified problem drinkers, who choose their own treatment goal (almost always reduced drinking). In these studies, generally a main effect of time is found, with reduced drinking in all categories. The second category of studies focused on neural mechanisms underlying CBM in AUD patients or on combined effects of CBM and neurostimulation, discussed in the next section.

# 4 Cognitive Bias Modification: Underlying (Neuro)Cognitive Mechanisms

The evidence presented above indicates that CBM can produce relevant change in AUD behavior. Given the historical background of CBM, as an experimental tool to directly manipulate a cognitive bias, in order to test its hypothetical effect on (symptoms of) psychopathological problems, it is a logical next step to test not only clinical outcomes but also underlying (neuro)cognitive mechanisms. While clinical outcomes of CBM as addition to AUD have been mostly positive (see Table 1), effects on cognitive biases have not consistently been observed. Especially mediation of the clinical outcome by the change in the cognitive process has only

Table 2 CBM with primary aims other than clinical outcome

			Control			Outcomes		
		Experimental group/	eroup/	Sessions/	Follow-			
Study	Sample	training (n)	training (n)		dn	Drinking	Task (s)	Remarks
ned at redu	Aimed at reducing drinking	60						
ers et al.	Problem	Web-based AAT	AAT50 sham   4 sessions	4 sessions	2-	FU: ×	_	Participants in all conditions
(2015a, b, c) drinkers	drinkers	(17) ATT100 Explicit	(24)		month			(including participants in the
	(130)	(27) ATT100 Implicit (35) ATT90 Implicit (33)						control-training condition) reduced their drinking
Cox et al.	Harmful	EG1: AtBM & LEAP (42)	Sham (29)	4 sessions/	-9	AC (post-	_	AtBM significantly reduced
(2015)	drinkers	EG2: LEAP (42)		4 weeks	month	test): ×		mean weekly drinking, but
	(148)	EG3: AtBM (35)				FU		only at the 3-month follow-up
						(3 months):		
						EG1:		
						AC		
						FU		
						(6 months):		
						EG1:		
						mean AC:		
						×, typical		
						AC↓		
Jones et al.	Heavy	Alc GNG (57)	Sham (54)	14 ses-	After	AC↓ (all	GNG: ×	No differences between
(2018)	drinkers	Alc Stop Signal (60)		sions/	training	groups)		groups
	(246)	General Inhibition (75)		4 weeks				
Strickland	AUD	cued GNG-ICT (145)	Arithmetic	14 ses-	2-week	AC↓	GNG: ×	Modest reductions in alcohol
et al. (2019)	recruited	WMT (150)	problems	sions/2		DD( (ICT		consumption, primarily in the
	online		(149)	weeks		> WMT>		ICT group
	(444)					CG)		
Van	Problem	GNG + AAT + VPT (49)	GNG + sham	12 ses-	-9	AC↓ (all	/	Web-based GNG-EMB,
Deursen	drinkers	GNG + AAT + sham VPT	ıam	sions/6	month	groups)		AAT-ApBM, VPT-AtBM,
(2019)	(427)	(58)	VPT (51)	weeks				added on a brief motivational
								(continued)

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			Control			Outcomes		
Study	Sample	Experimental group/ training (n)	group/ training (n)	Sessions/ time	Follow- up	Drinking	Task (s)	Remarks
		GNG + sham AAT + VPT (55) Sham GNG + AAT + VPT (47)	sham GNG + sham AAT + VPT (58) Sham GNG + AAT + sham VPT (57) Sham GNG + sham AAT + sham AAT + sham AAT					intervention No significant effects
Investigate neural effects	ural effects							
Wiers et al.	AUD	AAT-ApBM (15)	CG sham	6 sessions/	After		AAT: ×	fMRI
(2015a)	inpatients		(17)	3 weeks	training			EG: amygdala↓, nucleus
	(25)							accumbens: ×
								accumbens: ×
Wiers et al.	AUD	AAT-ApBM (13)	CG sham	6 sessions/	After		AAT: ×	fMRI
(2015b)	inpatients		(13)	3 weeks	training			EG: medial prefrontal
	(07)							cortex↓, nucleus accumbens: ×
								CG: medial prefrontal cortex:
								×, nucleus accumbens: ×
Martínez-	AUD (33)	A-CBM-ApBM (10)	No training	8 sessions/	After	_	AAT	Resting-state EEG
Maldonado		N-CBM-ApBM (12)	(11)	3 weeks	training		A-CBM:	A-CBM: alpha
et al. (2020)							ApB↓ N-CBM:	synchronization
							×	
Test interactions with brain stimulation	ns with brain	ı stimulation						

••	Ü	
tDCS combined with CBM showed a promising trend on treatment outcome in posthoc analysis		Short-lived effects: tDCS applied to DLPFC significantly increased abstinence rate, when combined with alcohol specific ICT, clinical outcomes might be better
AAT: All groups ApB↓	VPT: × IAT: ×	-
RR: EG <	FU: ×	RR (2 weeks): EG 13.9% < CG 36% RR (1 year): ×
1-year	1-year	1-year
4 sessions/ 1-year 1 week	4 sessions/ 1-year 1 week	5 sessions/ 5 days
Sham tDCS + ApBM (30) tDCS only (31)	Control ApBM + sham tDCS (22) Control ApBM + active tDCS (20)	neutral ICT + tDCS (28) neutral ICT + sham tDCS (34) ICT + sham tDCS (27)
ApBM + tDCS (30)	ApBM + sham tDCS (20) ApBM + active tDCS (21)	ICT (GNG) + tDCS (36)
AUD inpatients (91)	AUD patients (83)	AUD patients (125)
den Uyl AUD A et al. (2017) inpatients (91)	den Uyl AUD et al. (2018) patients (83)	Dubuson AUD et al. (2021) patients (125)

n number of subjects, EG experimental group, CG control group, Alc alcohol, ATT Action Tendency Training, LEAP Life Enhancement and Advancement Programme, ICT inhibitory control training, GNG GoNogo, WMT working memory training, A-CBM alcohol-related memory activation + CBM, N-CBM neutral memory activation + CBM, DD drinking days, RR relapse rate:: × = intervention showed no effect on outcome; † = increase; ↓ = decrease; AC alcohol consumption, FU follow-up, EMB evaluative memory bias seldomly been confirmed (Eberl et al. 2013), and was not supported in most published studies (Manning et al. 2021; Rinck et al. 2018; Salemink et al. 2021; Wiers et al. 2011, but see Gladwin et al. 2015). These largely negative findings could be due to the relatively poor reliability of bias assessment instruments, as discussed earlier. However, they could also indicate that we do not yet fully understand the mechanisms underlying CBM.

During the past decade, important basic research into cognitive mechanisms underlying CBM has been conducted. A specific bias in behavior (e.g., a relatively strong automatically activated tendency to approach-alcohol stimuli) can be assumed to reflect a mental-level bias (e.g., a stronger association between mental representations of alcohol and of approach actions). To the extent that CBM produces changes in this behavior, it can then be defined as a procedure that modifies this cognitive bias. Yet, it is important to understand that directly mapping (changes in) behavior onto (changes in) mental processes is problematic because it conflates the explanandum (i.e., the behavior that needs to be explained) with the explanans (i.e., the mental process with which one explains), as outlined in the functionalcognitive framework for psychological research (Hughes et al. 2016). Mental processes cannot be observed and thus can only be postulated to underlie behavior. As a result, scores on cognitive bias measurement tasks may well be explained in reference to mental processes other than originally considered. Similarly, changes in performance on these tasks (and related mediation of changes in clinical outcomes) on the basis of CBM may bear little relation to the targeted mental processes. To improve CBM (research), it is therefore important to strictly separate observable procedures and behavior (e.g., the observable bias in behavior) from explanation at the mental process level.

When CBM is defined at the procedural level (e.g., as a task that involves repeated avoidance of alcohol stimuli), theories about the mental mechanisms underlying its effects on behavior can be assessed objectively. CBM procedures typically involve conditioning (e.g., the repeated pairing of stimuli and responses) as inspired by the idea that these procedures directly change mental associations assumed to underlie addictive behavior (Phills et al. 2011; Smith and DeCoster 2000; Stacy and Wiers 2010). Yet, this associative explanation should not be taken for granted as conditioning effects do not require an associative explanation (De Houwer et al. 2020; Mitchell et al. 2009). In fact, one could argue that the bulk of scientific evidence may better fit alternative explanations (Corneille and Stahl 2018; De Houwer et al. 2020).

Accordingly, recent basic ApBM research (in healthy volunteers) suggests that its effects do not fit well with associative explanations (see Van Dessel et al. 2019 for an overview). For instance, associative theories of ApBM effects typically assume that ApBM contingencies produce automatic changes in mental associations that transfer into behavior. Yet, extensive ApBM training in healthy volunteers sometimes produces no behavior change (D. Becker et al. 2015; Cristea et al. 2016; Vandenbosch and de Houwer 2011), or even reversed effects (Mertens et al. 2018). In addition, effects may depend on unexpected boundary conditions such as the belief that ApBM helps to achieve desired outcomes (Van Dessel et al. 2019). Moreover,

change in behavior can be observed on the basis of mere instructions only (Van Dessel et al. 2015). Note that while these studies were experimental studies in human volunteers with artificial stimuli, instruction-based avoidance training has also been demonstrated in problem drinkers (Moritz et al. 2019) and in smokers, where imaginal training was related to reduced craving for cigarettes a year later (Gehlenborg et al. 2021), which emphasizes the real-world relevance of these insights into possible underlying mechanisms. There is also recent research demonstrating that mere observation of stimulus-action contingencies can have effects on approach-avoidance tendencies (Van Dessel et al. 2020), although these procedures do not involve the (repeated) experience of the contingencies that is thought to be required for association formation.

These basic findings into mechanisms underlying ApBM are more readily accommodated by recent theories that explain effects on the basis of inferential processes. From this perspective, ApBM can induce changes in the automatic inferences that underlie (pathological) behavior (Van Dessel et al. 2019). For instance, during alcohol-avoidance training, patients may learn to (automatically) infer that they are willing and able to avoid alcohol. This may facilitate the implementation of similar (avoidance) actions when confronted with similar contextual cues (i.e., alcoholic drinks) in the future. This perspective fits well with the core assumption of cognitive behavior therapy (CBT), the first-choice clinical treatment of AUD in Europe, that beliefs are central in psychological suffering, and it can be used to give directions for improvements of CBM. For instance, including goalrelevant consequences of approach-avoidance actions in a CBM procedure where participants are free to choose to approach or avoid addictive stimuli produces stronger CBM effects (Van Dessel et al. 2018). This will be elaborated below (ABC training). The inferential theory of ApBM effects has shown initial heuristic, predictive, and influence value, but more research is needed to examine its value in studies with clinical groups and with other types of CBM.

CBM effects can also be explained in reference to processes at the neural level. In one study, Corinde E. Wiers et al. (2015b) investigated effects of ApBM vs. sham training on neural cue reactivity. Patients in the active training condition showed greater reductions in alcohol cue reactivity in the amygdala bilaterally, and their decreases in the right amygdala activity correlated with decreases in craving; both effects were not observed for patients in the sham-training group. These results suggest that effects on neural cue reactivity are related to the clinical effects. However, it should be noted that in the small sample recruited for fMRI research (N = 32), there is minimal power to find a small clinical effect, which was indeed not found, and therefore the mediation hypothesis could not be tested.

The same research team also studied the neural correlates of the change in alcohol-approach bias after ApBM (C. E. Wiers et al. 2015a), by assessing the alcohol-approach bias in the scanner (with a special joystick device without metal, N=26). First, perhaps remarkably, an alcohol-approach bias was indeed found at the behavioral level. This is not self-evident for two reasons; first, as outlined above, not all alcohol-dependent patients show an approach bias (e.g., Piercy et al. 2021), and second, lying down can attenuate a neural approach reaction (Harmon-Jones and

Peterson 2009). Notably, the bias changed after ApBM at statistical trend level but not after sham training, similar to the findings of the large RCTs. The approach bias, and more specifically the alcohol pull vs. soft drink pull contrast, was related to mPFC activation. Moreover, this neural correlate of the alcohol-approach bias was more strongly reduced after ApBM training than after sham training. This reduction correlated with the behavioral change in alcohol-approach bias but not with craving. The mPFC has been related to the mental process of encoding motivational value (Hare et al. 2009, 2011), which could indicate that training helps to reduce the motivational value of alcohol, in addition to cue reactivity, which might also help to yield the add-on effects to treatment. For a review on neural correlates of CBM in general, see Wiers and Wiers (2017).

Relatedly, one area of recent research has been to add neurostimulation to CBM for AUD. It should be noted that neurostimulation has been investigated as a tool in addiction treatment by itself, with some promising recent findings (Harel et al. 2022; Zangen et al. 2021; reviews: Jansen et al. 2013; Luigies et al. 2019). Different types of non-invasive neurostimulation have been developed, including TMS (transcranial magnetic stimulation) and tDCS (transcranial direct current stimulation). The latter type of neurostimulation has been combined with varieties of CBM in AUD. It has the advantage that the equipment is not expensive and that an active control condition can be used, which starts with a brief stimulation (less than a minute), which people often subjectively feel as an itch, similar to active stimulation (which typically lasts 15–20 min). Different brain areas can be stimulated; here typically frontal areas are stimulated (see for details the reviews and specific papers). After a proof-of-principle study in hazardous drinkers (den Uyl et al. 2016), den Uyl and colleagues (2017) combined tDCS and ApBM in AUD patients. All patients (91 in the analytical sample) received ApBM; patients in one condition received active tDCS at the same time, which was compared with a condition in which patients received sham tDCS at the same time, and a condition in which patients received active tDCS and ApBM at different times, with the goal to investigate whether learning effects in CBM could be enhanced by active neurostimulation at the same time. There was some evidence for a faster decrease of the alcohol-approach bias in the combined tDCS and ApBM condition, but this only lasted the first sessions, and overall, the approach bias changed in all patients (who all received active ApBM). There was an indication of better clinical outcomes after a year in the combined group (at statistical trend level).

In a follow-up study (den Uyl et al. 2018), a full factorial design was used, combining active vs. sham tDCS with active vs. sham AtBM (N=98). The combined active training group showed a stronger negative attentional bias for alcohol (hence a stronger bias for non-alcoholic drinks) during the training sessions. No significant effects were found regarding craving (typically very low in inpatients), nor on relapse at 1-year follow-up. Finally, a recent study tested the combination of tDCS and selective inhibition (Dubuson et al. 2021), in a 2 × 2 factorial design (N=125). A main effect of tDCS was found on short-term relapse (2 weeks), with an indication that the combination with selective inhibition leads to the best outcomes. However, these effects did not persist longer. Altogether, these results

show promise for the combination of neurostimulation and CBM, but RCTs powered for the longer-term clinical outcomes are needed.

# 5 Other Types of Training in AUD Treatment: Working Memory, Mindfulness

The emphasis in this chapter has been on the current status of varieties of CBM, cognitive training employing disorder-related stimuli (here alcohol cues), as an add-on in the treatment of AUD. However, it should be noted that there are also more general types of training that have been employed in the context of AUD (see also Fig. 1). First, general (neuro-) cognitive functions have been trained, like working memory (WM), and some promising results have been obtained for this type of training, in self-identified problem drinkers (Houben et al. 2011b), in AUD patients (Snider et al. 2018), and in stimulant addiction (Bickel et al. 2011). However, contrary to the findings regarding CBM, there are no studies that reported significant improvements in clinical outcomes for WM training as add-on to treatment, and the largest RCT found no effects (Wanmaker et al. 2018). This is not to say that WM training is useless in the treatment of AUD; a moderated effect was found in self-identified problem drinkers (it reduced drinking in those who were relatively fast to associate positive things with alcohol, Houben et al. 2011b), reduced impulsivity was found after WM training in people with stimulant addiction (specifically, in delay discounting, Bickel et al. 2011), and an increase in future episodic thinking was found after WM training in AUD patients (Snider et al. 2018), which can be useful in the therapeutic process, as it can be helpful in planning life after treatment. Moreover, WM training can be useful because it can increase selfefficacy in patients: actively doing something to regain their (neuro-)cognitive potential can be therapeutically meaningful (Bates et al. 2013). However, the main problem with WM training in general (most research has been done in the context of ADHD) is the often-reported lack of generalization to real-life situations (Khemiri et al. 2019; Sonuga-Barke et al. 2013). This could be remediated by matching the therapeutic intervention to the increased abilities (e.g., once episodic memory has been increased, see for further comments, Wiers 2018).

An advantage of CBM in comparison with WM training (and other forms of general function training) is that addiction-related cues are already involved in the training, which may promote the generalization to real-life situations (e.g., change the initial reaction in a risk situation, as several patients reported after returning to everyday life following treatment including ApBM, such as not going to the beer section in the supermarket or immediately closing a fridge at a party when the fridge contains beer only). Another logical next step in this line of research would be to combine WM training with CBM, and at least one study of this kind is underway (Manning et al. 2019). A different way to train executive functions, more directly related to the therapy goals, is goal-management training, which has been combined

with mindfulness meditation exercise in two small studies in polysubstance users, with promising results (Alfonso et al. 2011; Valls-Serrano et al. 2016).

Mindfulness meditation can also be regarded as a form of (non-computerized) cognitive training. It can either be incorporated into existing programs (e.g., the "urge-surfing" exercise to resist craving can be easily incorporated into CBT for AUD, Ostafin and Marlatt 2008), which is similar to how CBM is used in AUD treatment (as an add-on to regular CBT-oriented therapy). However, mindfulnessbased therapy can also be a stand-alone therapy for SUDs. A recent systematic review concluded that mindfulness-based relapse prevention (MBRP) is as effective as existing evidence-based treatments for SUDs (Korecki et al. 2020). It should be noted, however, that there are several different mindfulness-based protocols for different SUDs in different stages (from indicated prevention to treatment, Korecki et al. 2020). There is ample evidence for effects on comorbid anxiety and depression symptoms (meta-analysis: Cavicchioli et al. 2018), and there are indications that the effects are partially mediated by reductions in stress and impulsivity (Korecki et al. 2020). Interesting from the perspective of this study is the finding that MBRP can lead to reduced attentional bias for substance cues (Garland et al. 2017; Spears et al. 2017, in chronic pain patients with opioid use problems and smoking cessation, respectively). A recent study found that effects of mindfulness increased after treatment in opioid-dependent pain patients (Garland et al. 2022), which contrasts with the typical effects of treatment (Cutler and Fishbain 2005), and CBM (Manning et al. 2022), which typically wear off. This could be related to the fact that patients can incorporate mindfulness exercises into their daily routines, also after treatment, which is not the case with the other interventions. Finally, regarding possible mechanisms in the context of this chapter, Ostafin and colleagues (2012) found that mindfulness training in heavy drinkers decoupled the predictive power of alcohol-approach associations (as assessed with an IAT) from the heavy drinking behavior: Before mindfulness training, the IAT score was predictive; after training this was no longer the case. This suggests a different mechanism than ApBM, where it has been found that the training changes the IAT scores from predominantly alcohol approach to alcohol avoid, both in heavy drinkers (Wiers et al. 2010) and in AUD patients (Wiers et al. 2011). We know of no studies combining MBRP and CBM, but this could also be an interesting avenue for further research (cf., Larsen et al. 2021).

# 6 Cognitive Training in (Alcohol) Addiction: New Avenues for Improvement

In addition to the avenues sketched above (combinations with general training or mindfulness and neurostimulation), there are two avenues for further research that we briefly discuss: gamification, and a new variety of training, based on emerging insights into underlying cognitive mechanisms: ABC training.

First, varieties of gamification and VR have been introduced to make CBM more attractive (or less boring) to users. This has been used primarily to make training more attractive to young substance users, in a series of studies by Boendermaker and colleagues (2015a, 2017, 2018). Results were modest, which may have been related to the target of gamification: to increase motivation to perform the training, but this in itself does not change the motivation to change the addictive behavior (e.g., binge drinking) in real life (Boendermaker et al. 2015b). In an as-yet unpublished study in AUD patients, gamified training did not outperform results of standard training; in fact, there were indications of reduced efficacy (Boffo et al. in preparation). Further, a recent RCT in patients with AUD or CUD used a gamified AtBM paradigm and found no differences with sham training (Heitmann et al. 2021), while effects have been found in AUD patients with regular ("boring") AtBM (Rinck et al. 2018; Schoenmakers et al. 2010). In conclusion, while gamification of CBM seems like a logical next step, results so far have not been very supportive, and we should not assume that it works better than traditional CBM, just because it looks more attractive. In addition to gamification (or as a gamification element), one could also bring in social elements, such as quitting together and supporting each other, not only an important element in the AA approach, but also an element in successful smoking cessation programs, when combined with contingency management (Van Den Brand et al. 2018). Contingency management (in essence using operant conditioning techniques: rewarding desired behavior such as producing drug-free urine) has been shown to be effective in different addictions, but the effects mostly disappear after discontinuing the rewards (meta-analysis: Benishek et al. 2014). For this reason, it is interesting to combine it with other elements, such as social reinforcement (Van Den Brand et al. 2018), and it could also be tried in combination with other interventions such as motivational interviewing and CBM in groups for which change is difficult to obtain, such as smoking adolescents (Kong et al. 2015). Some other studies have pioneered virtual reality (VR) versions of CBM, with first proof-of-principle studies in anxiety (Otkhmezuri et al. 2019), smoking (de Bruijn et al. 2021), and AUD (Eiler et al. 2020), which could also be used in more gamified varieties of CBM or in the conceptually new ABC training, described next.

Based on new insights into the cognitive mechanisms underlying ApBM, described above, a new variety of CBM has been proposed: ABC training (Wiers et al. 2020). CBM (including ApBM) was originally based on dual process models, either general models referring to cognitive processes in decision making and health behaviors (e.g., Hofmann et al. 2009; Strack and Deutsch 2004) or more specific models of addiction (e.g., Bechara 2005; Wiers et al. 2007). The general idea was that CBM could change relatively automatic or impulsive processes, which would provide an important addition to influencing the more reflective processes targeted in therapy (e.g., Friese et al. 2011). However, dual process models have been criticized on theoretical grounds; for example, the impulsive and reflective system cannot readily be dissociated and specific processes typically demonstrate a mixture of impulsive and reflective processes (Gladwin et al. 2011; Hommel and Wiers 2017; Keren and Schul 2009; Kruglanski and Gigerenzer 2011; Melnikoff and Bargh 2018). In addition, basic research on cognitive mechanisms underlying ApBM has

demonstrated that conscious awareness is necessary, that effects can be obtained by instruction only, and that the effects depend on important moderators such as beliefs about the implications of the learned relation, like the belief that avoiding alcohol helps to refrain from drinking (see Sect. 4, and for a review: Van Dessel et al. 2019). These results are more in line with an alternative framework: that of inferential (predictive) processing, delineated in well-supported state-of-the-art theories in cognitive neuro(science) such as predictive processing theories (Clark 2013; e.g., Friston 2010; see for an application to addiction, Wiers and Verschure 2021). From this perspective, ApBM does not produce changes in mental associations, but impacts propositional processes. Specifically, the contingencies between a stimulus, a response, and an outcome can evoke inferences (e.g., repeated avoidance of alcohol that leads to positive consequences → 'I want to avoid alcohol') that influence (addictive) behavior. It is assumed that all behavior is the result of the context-dependent activation of goals and inferences to achieve these goals. Note that, from this perspective, addictive behavior is goal-directed (see also Moors et al. 2017); however, the context may sometimes activate goals that lead to inferences that evoke pathological behavior and contrast with other, typically more long-term goals (e.g., health, relationships). In ABC training, these inferences are targeted more directly.

The ABC training procedure involves personally relevant antecedents (A), behaviors (B), and consequences (C). Contextual cues are important in addiction, and ABC training therefore aims to promote that relevant cues come to trigger not the addictive behavior but a personally relevant alternative behavior (B). This pattern is repeatedly practiced on the basis of consequences (Cs) that are relevant for the participant (or patient) such that the participants may learn to (automatically) infer that they will perform alternative behavior in risk situations, given the relevant positive consequences. This approach closely aligns with CBT for addiction, but adds a personalized training, in which participants repeatedly emit personally relevant alternative behaviors in risk situations, in relation to the consequences.

More specifically, in ABC training, participants are first helped to identify (1) personally relevant antecedents (e.g., coming home stressed) of the SUD, (2) alternative behaviors (Bs) that could be performed in that situation (e.g., go out for a walk, drink tea), and (3) relevant consequences of both behaviors (e.g., changes in health, money). For a given A, participants then perform training in three stages. In the first practice stage, participants react to a feature of the stimulus unrelated to the contents, and approach either the SUD-relevant stimulus or the alternative stimulus, similar to the first phase in CBM. However, the goal here is to make the personally relevant consequences of the different choices salient; for example, when the substance is approached, bars that indicate achievement of health or money goals go down, and when the alternative is performed (e.g., go for a walk), they go up. In the second slow free choice phase, participants choose themselves what they want to do in a limited set of contexts (As), and the consequences of their choices are always shown. In the third phase, participants do the same exercise under time pressure (personalized time window).

While there are no finished trials of ABC training yet, there are positive indications of potential effectiveness. First, two studies using personalized alternative behaviors in smokers found promising results (Kopetz et al. 2017; Wen et al. 2021). Second, a series of studies of ApBM including consequences in healthy students in the domain of healthy eating found better results than for regular ApBM without consequences (Van Dessel et al. 2018). Third, an as-yet unpublished first set of studies testing ABC training in healthy volunteers found promising effects (increased automatically activated negative expectancies after training compared with control training), as did a first study in volunteers of an abstinence challenge (increased rate of abstinence during the challenge compared to both traditional CBM and sham CBM). Clearly, next steps include optimizing the new intervention and testing it in AUD patients, in comparison with "traditional" ApBM.

ABC-training interventions fit well with current practice in CBT where patients learn to build new patterns of thinking (Beck and Dozois 2011). It provides patients with a context in which they can gradually gather evidence to learn these patterns and automatize their application, building on the state of the art in (cognitive) science. While this approach seems promising, ABC-training interventions still require extensive testing in studies to determine their optimal format (e.g., training in personally relevant 3D, VR, or real-life environments) and in well-designed randomized clinical trials to assess their clinical effectiveness.

#### 7 Conclusion

Approach bias modification (ApBM) is the form of cognitive bias modification (CBM) for which most evidence has been obtained that it can be of value as an add-on in the treatment of AUD. Across multiple large RCTs, it has been found that long-term abstinence is reduced by approximately 10% when ApBM is added to treatment. It should be noted that there are also promising findings regarding other forms of CBM, such as attentional bias modification (AtBM) and selective inhibition (in the variety where rare alcohol stimuli are always inhibited), and to some extent for other forms of cognitive training such as working memory training (although not regarding the primary outcome change in addictive behaviors), as well as for non-computerized mental training in the form of mindfulness meditation.

Regarding cognitive mechanisms underlying effects of ApBM, recent research has found evidence in favor of inferential processing, rather than the associative mechanisms proposed in dual process models (e.g., effects depend on conscious awareness and expectancies, and can be achieved to some extent through instructions only). These emerging insights have led to a new variety of CBM: ABC training, which is currently tested regarding efficacy.

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