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# Imaging the neural effects of cognitive bias modification training

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ABSTRACT

Cognitive bias modification (CBM) was first developed as an experimental tool to examine the causal role of cognitive biases, and later developed into complementary interventions in experimental psychopathology research. CBM involves the "re-training" of implicit biases by means of multiple trials of computerized tasks, and has been demonstrated to change anxious, depressive and drug-seeking behavior, including clinically relevant effects. Recently, the field has progressed by combining CBM with neuroimaging techniques, which provides insight into neural mechanisms underlying how CBM affects implicit biases in anxiety, depression, and addiction, and potentially other pathologies. This narrative literature review summarizes the state of the art of studies on the neural effects of CBM and provides directions for future research in the field. A total of 13 published studies were found and discussed: $n = 9$ in anxiety, $n = 2$ in depressive behavior, and $n = 2$ in addiction.

## Introduction

Cognitive bias modification training (CBM) refers to computerized tasks that aim to re-train cognitive biases. Cognitive biases are a broad class of automatically activated processes that may persist even when they conflict with conscious goals. For example, the attention of an individual addicted to alcohol may be captured by an alcohol cue, and the same cue may elicit an action tendency to approach the stimulus (Wiers et al., 2007), while the same patient may hold conscious beliefs that these drinks should be avoided to avoid further harms. For individuals with depressive symptoms (both clinical and non-clinical) a bias toward negative stimuli has been reported (Peckham et al., 2010), and a core feature of people with anxieties (clinical and non-clinical) is increased attention for threat-relevant cues, i.e., an attentional bias or vigilance for threatening stimuli (meta-analysis: Bar-Haim et al., 2007).

### *Measuring cognitive biases*

Cognitive biases can be tested with computer-based tasks, and may be considered "automatic" if task instructions are indirect (i.e., if participants are largely unaware of the task's outcome measures (but see Gawronski et al., 2006), or if the outcome measures involve subtle behavioral effects that are not directly under conscious control (De Houwer, 2006; Stacy and Wiers, 2010)). Automatic measures may be less susceptible to social desirability than explicit measures, such as subjective craving (De Houwer, 2006). The most frequently used task for attentional biases is the Dot Probe Task, in which pairs of target-relevant (e.g., emotionally or drug-related) and neutral images are presented on a computer screen for a brief period of time (typically 500 ms) (MacLeod et al., 2002). A probe-stimulus is then presented at the location of one of the cues, and participants are required to identify the probe (originally, the probe consisted of one or two dots) using button presses. When participants tend to be relatively fast to respond to probes appearing at the position of the disorder-relevant pictures, this can be used as a measure for an attentional bias toward that stimulus category. For example, drug abusers have been shown to fixate longer on drug-related cues than neutral cues (Field et al., 2013), but negative findings have also been reported (Townshend and Duka, 2007; Wiers et al., 2016) and temporal dynamics strongly modulate the bias (Noel et al., 2006; Townshend and Duka, 2007; Vollstadt-Klein et al., 2009). Anxiety is related to fast attentional bias toward threat, likely in a complex, time-dependent fashion (Bar-Haim et al., 2007; Koster et al., 2006; MacLeod and Mathews, 1988; Mogg et al., 2004). Individuals with depression have also shown stronger attention biases toward negative stimuli on the dot probe task compared to controls (Peckham et al., 2010), which is most consistently observed for cues that are presented for longer than a second (De Raedt and Koster, 2010). Biased action-tendencies can be assessed with the Approach Avoidance Task (AAT) in which participants push and pull pictorial

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cues (target-relevant/neutral) with a joystick (Rinck and Becker, 2007). Individuals with social anxiety (Heuer et al., 2007; Roelofs et al., 2010), and depression (Seidel et al., 2010) have been shown to faster avoid than approach emotional facial cues than controls, whereas heavy drinkers (Wiers et al., 2009), patients with alcohol use disorder (AUD) (Ernst et al., 2014; Wiers et al., 2014), heroin abusers (Zhou et al., 2012), and heavy cannabis users (Cousijn et al., 2011) have been shown to faster approach than avoid drug cues compared to non-addicted control groups. Since cognitive biases have been found to be correlated with a variety of psychopathological problems (Williams et al., 1996), including explicit craving scores in drug users (Mogg et al., 2005; Wiers et al., 2013a), anxiety scores (Bar-Haim et al., 2007), and depression severity (Beevers et al., 2011), these biases may be clinically relevant outcome measures. Bar-Haim and colleagues, however, found that for PTSD, greater attentional threat avoidance predicted greater PTSD symptoms (Sipos et al., 2014; Wald et al., 2013), which makes the clinical efficacy of avoiding threat CBM interventions questionable for this disorder. While many other cognitive biases have also been identified in various psychopathologies (e.g., interpretive biases, expectancy bias, recall bias), the current review will focus specifically on those that have been investigated in conjunction with neuroimaging: the attentional and approach bias.

*Behavioral and clinical effects of CBM*

Even more interesting is the possibility that cognitive biases not only correlate with but also cause mental health problems. The first CBM interventions were designed to directly manipulate cognitive biases in psychopathology, with the primary goal of testing causality of the bias for problem-behaviors (MacLeod et al., 2002; Mathews and Mackintosh, 2000). Tasks were adapted in order to directly manipulate the cognitive bias and study effects on behavior. People can be trained either toward the disorder-relevant cues (e.g., threat or alcohol cues), which typically increases disorder-relevant symptoms or away from the disorder-relevant cues, which reduces disorder-relevant symptoms (Field and Eastwood, 2005; MacLeod et al., 2002). In clinical samples, training away from the disorder-relevant stimuli is usually compared with a condition in which no contingency is changed, i.e., continued assessment. For example, Field et al. (2009a) aimed to manipulate smokers' attentional biases for smoking cues by always pairing the probe with neutral cues (“avoid smoking”), always with smoking cues (“attend smoking”) or probes were paired with the two categories with equal probability (control group, no change). The manipulation decreased, increased and did not change participants' attentional biases for smoking cues respectively (Field et al., 2009a). Regarding smoking, a recent study found that repeated attentional retraining helped heavy smokers to succeed in their quit attempt, doubling the chance to successfully abstain from smoking half a year later (Elfeddali et al., in press).

Manipulation of approach biases have used training versions of the AAT, in which task-irrelevant display features of stimuli were selectively approached or avoided. For example, patients with AUD were trained to push alcohol cues more frequently than soft drink cues, by manipulating the format of the cues (landscape or portrait), according to which participants were instructed to push/pull (Wiers et al., 2011). In this way, one group of patients systematically pushed alcohol cues away, and pulled non-alcoholic beverages, while another group equally often pushed and pulled alcohol and soft drinks or did not train at all (Eberl et al., 2013; Wiers et al., 2011). CBM tasks have often (but not always) been found to change the targeted cognitive biases, and when they did, often (but not always) the relevant behavior was also influenced (Clarke et al., 2014b). For example, changing an approach-bias for alcohol resulted in reductions in drinking in students (Wiers et al., 2010) and in relapse in patients with AUD (Eberl et al., 2013; Wiers et al., 2011; Manning et al., 2016). CBM has further shown clinical effects for treatment in anxiety (Amir et al., 2009; Linetzky et al., 2015; Schmidt et al., 2009), depression (Peckham et al., 2010) and addiction (Eberl et al., 2013; Schoenmakers et al., 2010; Wiers et al., 2011). Despite studies reporting negative results of CBM in student samples (Field et al., 2007; Schoenmakers et al., 2007) and a critical meta-analysis of effects in anxiety (Cristea et al., 2015), there is evidence that CBM helps at least a subgroup of patients with anxiety and addiction problems (Linetzky et al., 2015; Wiers et al., 2013b). The relevant question for such applications appears not to be whether CBM works in general, but when it works, for instance in relation to motivation (Gladwin et al., 2016). However, evidence of behavioral effects of CBM in depression has been relatively weak so far (Hallion and Ruscio, 2011). In summary, while results in student-samples and in internet-trials have been weak, there is substantial evidence that varieties of CBM can produce clinically meaningful effects in patients with alcohol dependence and in patients with anxiety.

Given the state of affairs in addiction, where several studies found a clinically relevant add-on effect of CBM when combined with CBT (Eberl et al., 2013; Schoenmakers et al., 2010; Wiers et al., 2011), and no differential training effect was found for CBM alone (Lindgren et al., 2015; Wiers et al., 2015c), it appears likely that CBM affects different processes than CBT. Theoretically, CBT (especially when combined with motivational interviewing) provides an alternative long-term perspective to continued alcohol or drug use, and some strategic techniques to accomplish that goal. However, for some patients increased motivation and strategies are not enough when faced with conditioned stimuli related to their addiction, and triggering a cascade of appetitive processes (attentional bias, positive memory associations, approach bias), especially when control is suboptimal, e.g., under conditions of stress or fatigue. For those patients, CBM appears to be a helpful add-on to CBT. Nevertheless, applying CBM without also addressing long-term motivation to change behavior appears to have little chance of success (Kerst and Waters, 2014; Lindgren et al., 2015).

*Neural processes underlying cognitive biases*

There is a growing literature on neural correlates of cognitive bias in anxiety, depression and addiction at “baseline”, before CBM training. For anxiety, performance on the dot probe task has been consistently associated with perturbed activation in brain regions involved with emotional processing (i.e., the amygdala) and attentional control (i.e., the lateral prefrontal cortex and anterior cingulate) (White et al., 2016). That is, anxious individuals have shown increased activation on the anxiety Dot Probe task in the amygdala (Monk et al., 2006), lateral PFC (Britton et al., 2012; Telzer et al., 2008) and dorsal anterior cingulate (dACC) (Choi et al., 2016; Price et al., 2014). Anxiety has also been associated with impaired connectivity of frontal cortical regions with the amygdala (Carlson et al., 2013; Hardee et al., 2013) and with the (para)hippocampus (Price et al., 2014), suggesting impaired attentional control to the exposure of threat Various EEG studies suggest a brain circuitry involved in rapid responses to threat in anxiety, including greater amplitudes of early components (P2 and *C*1) to threat faces in high- versus low anxious individuals (Bar-Haim et al., 2005; Eldar et al., 2010). For depression, a similar role of altered PFC function during biased attention for negative stimuli has been suggested. Individuals with high symptoms of depression indeed showed weaker activation in the lateral PFC when shifting attention away from negative stimuli, than individuals with few symptoms (Beevers et al., 2010). An imbalance between bottom-up and top-down neuronal circuits has been proposed in addiction (Volkow et al., 2013). In abstinent patients with AUD, the alcohol approach bias was associated with an increased response in the nucleus accumbens (NAcc), and medial prefrontal cortex (mPFC) compared to controls (Ernst et al., 2014; Wiers et al., 2014). Activation in the amygdala was further positively associated with craving within the alcohol group (Wiers et al., 2014). Moreover, alcohol attentional bias scores correlated with alcohol-cue induced activation in mesocorticolimbic reward system in

patients with AUD (Vollstadt-Klein et al., 2012) and in a student population, some evidence was found that hazardous drinking is related to a lack of protective attentional inhibition related to the precuneus (Gladwin et al., 2013). In smokers compared to controls, dACC and frontal regions showed increased activation on an attentional bias task for smoking cues, suggesting that more top-down attentional resources are needed (Hester and Luijten, 2014; Luijten et al., 2011).

Test-retest reliabilities on behavioral performances on attentional bias tasks have been relatively poor (Schmukle, 2005; White et al., 2016), and in general, one can state that implicit or indirect tasks in which participants react to a feature unrelated to the contents, have a poorer reliability than tasks where people react to a contents-related feature of the stimulus (De Houwer, 2003). Interestingly, however, physiological measures may provide more reliable measures, for example eye-movements for attentional bias (Field et al., 2009b) and a recent study found good reliability of neural responses to a Dot Probe Task in ventrolateral PFC and fronto-amygdala connectivity (White et al., 2016). The latter study highlights potential for neuroimaging research over behavioral measures in studies in which a task is used multiple times. Such findings provide suggestions on where neural effects of CBM might be found.

### *Hypothesized working mechanisms of CBM*

The question remains as to what the working mechanisms of CBM are. What are the changes in brain activity associated with CBM training? Which neural mechanisms underlie its effectiveness in changing behavior and clinically relevant effects? The effects of CBM have been proposed to either influence top-down attentional control or bottom-up attention processes, or both (Britton et al., 2015; Wiers et al. 2015b). The lateral PFC, a key region involved in cognitive control especially when participants have to inhibit competing responses (Aron and Poldrack, 2005; Helfinstein et al., 2014), and which has shown to play a significant role in modulating attentional biases for emotional information (Beevers et al., 2010; Britton et al., 2012; Telzer et al., 2008; White et al., 2016), is hypothesized to enhance in strength after CBM. Prior research shows that the lateral PFC is involved in the cognitive regulation of emotional information on other cognitive tasks (Bechara, 2005; Ochsner and Gross, 2005) and control of drug craving (Hayashi et al., 2013; Goldstein and Volkow, 2011). Another brain area that is a key candidate for the effects of CBM on is the dACC, which is involved in the monitoring and resolving potential emotional conflicts on attentional bias tasks (Choi et al., 2016; Etkin et al., 2006; Hester and Luijten, 2014; Luijten et al., 2011) and has been shown to be active in the regulation of craving by reappraisal in smokers (Zhao et al., 2012). Moreover, pharmacological treatment decreased ACC activation on an attentional bias task in patients with schizophrenia and cannabis use disorder (Machielsen et al., 2014). CBM may therefore normalize dACC activations on attentional and/or approach bias tasks. Stimulation of the lateral PFC and ACC with neuromodulation techniques such as transcranial direct current stimulation (tDCS) has been used to increase control mechanisms necessary for successful inhibitions (Conti and Nakamura-Palacios, 2014; Heeren et al., 2015). First promising studies combining tDCS and CBM may modulate neural circuits associated with CBM (e.g., Clarke et al., 2014a), and are discussed as a future research direction at the end of this review.

On the other hand, limbic brain activations to previously emotional (e.g., amygdala for anxiety) or rewarding (e.g., amygdala and NAcc for addiction) cues are hypothesized to reduce after CBM. The amygdala plays a central role in the modulation of incentive salience to cues (Cunningham and Brosch, 2012), the formation and consolidation of emotional memories and in Pavlovian conditioned learning (Koob and Volkow, 2010; Mahler and Berridge, 2009). As discussed in the previous paragraph, the amygdala has played a strong role in the anxiety attentional bias (Carlson et al., 2013; Hardee et al., 2013; Monk et al., 2006), and often correlates with craving in patients with AUD (Wiers and Heinz, 2015; Wiers et al., 2014). Behavioral studies of inhibition training showed that the inhibition of responses to stimuli that were initially positively valenced resulted in a devaluation of this stimulus category (Veling and Aarts, 2009; Veling et al., 2008). CBM trains participants to repeatedly perform actions that are incongruent with an established cognitive bias, which may lead to a similar effect of modulating the overall salience of target-related anxious, negative or drug-related cues encoded in limbic structures such as the amygdala (Mahler and Berridge, 2009, 2012; Wiers et al., 2013c). Previous studies with both cognitive behavioral therapy (CBT) and pharmacological interventions have altered both frontal and limbic brain areas during performance of a Dot Probe task incorporating anxious faces in participants with generalized anxiety disorders (Maslowsky et al., 2010). Additionally, such neural correlates may also predict responses to CBM, which has been shown for behavioral therapy in anxious individuals (Ball et al., 2014).

## Studies investigating the neural effects of CBM

This review summarizes studies that investigate the effects of behavioral CBM on neural processing including EEG and task-based and resting state magnetic resonance imaging (MRI). At the time of writing there are, to the best of our knowledge, 13 published articles that study the neural effects of CBM using EEG and functional MRI. Nine studies investigated the effects on anxious behavior; two on depressive symptoms and two studies were performed in patients with AUD. Study designs including participants, training/imaging tasks used and results are summarized in Table 1.

Abbreviations: AAT = approach avoidance task; AUD = alcohol use disorder; CBM = cognitive bias modification; BDI = Beck's depression index; BOLD = blood-oxygen-level-dependent; dACC = dorsal anterior cingulate; DAQ = desire for alcohol questionnaire; ERP = event-related potential; fMRI = functional magnetic resonance imaging; LSAS = Liebowitz social anxiety scale; MDD = Major Depressive Disorder; mPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; PFC = Prefrontal cortex; SAD = Social Anxiety Disorder; SMA = supplementary motor area; STAI = state trait anxiety index; 3 T = 3 Tesla.

### *Neural effects of CBM in anxiety*

#### *EEG*

The first study that investigated the neural effects of CBM (Eldar and Bar-Haim, 2010) was performed in 30 anxious and 30 healthy non-anxious controls (top and bottom quartiles based on STAI state scores; Spielberger et al., 1983), and tested the effects of a single session of a Dot probe-based CBM (480 trials) on Dot Probe performance while being scanned with EEG. Groups were evenly allocated to either a condition in which their attention was trained away from threat signals or a placebo training with threat signals away/toward in equal probability. The results revealed that CBM reduced behavioral bias scores in anxious participants only. For event-related potential (ERP) measures, CBM in anxious participants reduced P2 and P3 amplitudes, which are components involved in face processing. CBM further enhanced N2 amplitudes in anxious individuals, which is involved in attention control processes, whereas placebo training decreased N2. Last, P3 amplitudes decreased over training in non-anxious (CBM/placebo) and anxious participants (CBM only), which suggests that anxious participants in the placebo condition failed to habituate high level processes of attention orienting. That is, frontal P3 has been shown to decrease when participants are repeatedly exposed to stimuli, i.e., in habit formation. Altogether, these data suggest that CBM enhances top down control processes in emotional processing rather than bottom-up attentional processes.

A second ERP study also studied the effects of a Dot Probe-based CBM on Dot Probe performance with EEG, but this time in healthy

**Table 1**
Studies combining CBM and neuroimaging for anxiety (purple rows), depressive mood (blue) and alcohol dependence (orange) before training ("pre"), after training ("post") or the comparison of before and after training ("pre-post").

| Authors (year) | Study group | Training type | Imaging task | Results |
|---|---|---|---|---|
| 1.1 Neural effects of CBM in anxiety: EEG | | | | |
| Eldar and Bar-Haim (2010) | $n$ = 30 adults with high anxiety scores, $n$ = 30 healthy non-anxious adults (top and bottom quartiles of STAI scores) | 1 session of Dot Probe CBM angry/neutral faces:<br>(1) $n$ = 15 anxious subjects, avoid threat<br>(2) $n$ = 15 non-anxious, avoid threat<br>(3) $n$ = 15 anxious, 50/50 placebo<br>(4) $n$ = 15 non-anxious, 50/50 placebo<br>(480 trials) | Pre and post training: Dot Probe with angry/neutral faces (144 trials: 48 neutral-neutral, 96 angry-neutral)<br>(EEG) | - Anxious participants in avoid threat training group reduced behavioral bias<br>- Training decreased P2 amplitude in anxious participants<br>- Training increased N2 amplitude in anxious participants<br>- Training decreased P3 amplitude in anxious participants |
| O'Toole and Dennis (2012) | $N$ = 49 healthy non-anxious adults | 1 sessions of Dot Probe CBM: (1) $n$ = 25 attention toward threat<br>(2) $n$ = 24 attention away from threat<br>(480 trials) | Pre and post training: Dot Probe with angry, happy and neutral faces, 100 or 500 ms; 288 trials<br>(EEG) | - CBM changed behavioral bias, but only in participants who showed pre-training biases<br>- The away-from versus toward-threat CBM decreased P1 amplitudes to faces presented for 100 ms and to non-threatening faces |
| Suway et al. (2013) | $N$ = 34 non-anxious female participants | 1 sessions of Dot Probe CBM: (1) $n$ = 12 attention toward threat<br>(2) $n$ = 16 50/50 placebo training<br>(600 trials) | Pre and post training: Dot Probe to threat 100 trials, 500 ms<br>(EEG) | - CBM increased P2 amplitude compared to Placebo<br>- Training toward threat caused greater depression vulnerability to a stressor |
| 1.2 Neural effects of CBM in anxiety: fMRI | | | | |
| Browning et al. (2010) | $N$ = 29 healthy volunteers | 1 sessions of Dot probe CBM with negative and neutral words:<br>(1) $n$ = 15 100% threat avoid<br>(2) $n$ = 14 100% threat attend<br>(576 trials) | Post training: Pessoa task with fearful and neutral faces. Presentation time max 4 s; 160 trials<br>(3 T fMRI) | - Greater lateral PFC activation when direction of participants' attention was contrary to their training<br>- Connectivity analyses showed the identified lateral frontal regions were influencing attention as indexed by activity in visual association cortex |
| Taylor et al. (2014) | $N$ = 14 healthy participants with elevated social anxiety<br>(> 40 on LSAS) | 1 session of Dot Probe CBM:<br>$N$ = 14 80% neutral-threat, 20% neutral-neutral, 500 ms (360 trials) | Pre and post training: emotional face task: faces versus shapes<br>(3 T fMRI) | - Pre-post: decreased activation in bilateral amygdala, insula and mpFC (subgenual anterior cingulate cortex), but increased in mPFC/OFC and visual cortex<br>- Post: Greater mPFC activation ~ reduced attentional allocation for threat & anxiety reactivity to stressor |
| Mansson et al. (2013) | $N$ = 11<br>participants with SAD | 8 sessions<br>(4 weeks) of internet-delivered Dot Probe CBM by $N$ = 11 with 100% avoid disgust versus neutral faces (500 ms)<br>(1280 trials) | Pre and post training: Affective face processing task: anger, fear, surprise, neutral faces<br>(3 T fMRI) | - Pre-post: increased activation in bilateral amygdala (FWE-corrected) and postcentral gyrus, putamen, SMA, temporal superior ($p$ < 0.001) (whereas the reverse pattern was shown for a group with cognitive behavioral therapy) |
| Mansson et al. (2015) | $N$ = 26 participants with SAD | 8 sessions<br>(4 weeks) of combined internet-based CBT and Dot Probe CBM by $N$ = 26 with 80% neutral-disgust and 20% neutral-neutral facial expressions<br>(480 trials) | Pre training: self-referential criticism task reading 216 sentences with positive/negative/neutral valence<br>(3 T fMRI) | - Pre-training dACC and amygdala activation to self-referential criticism (self > other referred criticism) predicted 1-year treatment response<br>- dACC was less reactive to self-referential criticism in responders than non-responders<br>- Reduced dACC-amygdala coupling at pre-treatment in responders versus non-responders |
| Mansson et al. (2016) | $N$ = 26 CBM ($n$ = 13 participants with SAD, $n$ = 13 healthy controls)<br><br>$N$ = 26 CBT<br>($n$ = 13 participants with SAD, $n$ = 13 healthy controls) | 8 sessions<br>(4 weeks) of Internet delivered Dot Probe CBM<br>(1) $n$ = 13 SAD<br>(2) $n$ = 13 healthy controls.<br><br>CBT group underwent 4 weeks of CBT | Pre and post training: self-referential criticism task reading 216 sentences with positive/negative/neutral valence<br>(3 T fMRI) | - No direct report of SAD versus control comparison of pre-post CBM effects<br>- CBM was used as control for CBT: while CBT decreased bilateral amygdala gray matter volume and amygdala activation for self-criticism, there was no effect of CBM (or even more a tendency of increased amygdala volume/activation; statistics missing from article) |
| Britton et al. (2015) | $N$ = 30 Healthy participants with social anxiety symptoms (> 45 on LSAS) | 8 sessions<br>(4 weeks) of Dot Probe CBM;<br>(1) $n$ = 15 active CBM (100% threat away),<br>(2) $n$ = 15 placebo CBM (50% threat away)<br>(1280 trials), plus 480 training trials in scanner: CBM 80% threat away; 50/50 placebo | Pre, post-acute and post-extended training: Dot Probe task with angry/neutral faces<br>(threat incongruent > threat congruent); 500 ms; 144 trials (3 T fMRI) | - CBM decreased social anxiety symptoms<br>- Group × time × condition: decreased activation in bilateral amygdala<br>- Greater baseline left amygdala activation predicted social anxiety symptoms reductions; irrespective of group assignment |

*(continued on next page)*

**Table 1** *(continued)*

| Authors (year) | Study group | Training type | Imaging task | Results |
|---|---|---|---|---|
| 2. Neural effects of retraining depressive behavior: fMRI | | | | |
| Beevers et al. (2015) | *N* = 44 adults with MDD | 8 times<br>(4 weeks) of Dot Probe CBM<br>(1) *n* = 24 active CBM (85% dysphoric images away)<br>(2) *n* = 20 placebo (50% neutral/50% dysphoric) | Pre and post training: Resting state (3 T fMRI)<br>Behavioral Dot Probe task with happy/sad/neutral faces (500 ms) | - Pre-post: CBM reduced negative attention bias and increased resting state functional connectivity between middle frontal gyrus and dACC, compared to placebo<br>- No group × training effects in depressive symptom<br>- Pre-post change in attention bias was correlated with change in depression symptoms in CBM group only<br>- Exploratory results show that for placebo-training, pre-post changes in connectivity in precuneus, medial frontal gyrus contributed to symptom improvement |
| Li et al. (2016) | *n* = 41 women with subthreshold depression (BDI > 14)<br>*n* = 26 matched non-depressed controls | 28 sessions<br>(4 weeks) of Dot Probe CBM<br>(1) *n* = 24 active CBM (87.5% toward positive)<br>(2) *n* = 17 placebo (50% positive/negative) with positive, neutral and negative (sad/angry) faces | Resting state: pre/post for depressive group, once for controls<br>(3 T fMRI) | - Pre-post: CBM decreased depressive symptoms and increased attention for positive stimuli<br>- Pre-post: CBM reduced amplitude of low-frequency fluctuations of the right insula and right middle frontal gyrus; which showed greater fluctuations than in non-depressed subjects<br>- Functional connectivity decreased between right insula and fronto-insular and supramarginal gyrus pre-post CBM training, which was associated with improvement of depressive symptoms |
| 3. Neural effects of CBM in addiction: fMRI | | | | |
| Wiers et al. (2015b) | *N* = 32 abstinent inpatients with AUD | 6 sessions<br>(3 weeks) of AAT-based CBM:<br>(1) *n* = 15 CBM alcohol push/pull (90%/10%)<br>(2) *n* = 17 placebo alcohol push/pull (50/50)<br>(400 trials) | Alcohol cue reactivity with alcohol and soft drink cues<br>(3 T fMRI) | - Pre-post behavioral bias: no significant interaction effect of group by time; no main effects.<br>- Pre-post cue reactivity: stronger reductions in alcohol cue-induced cue reactivity in the amygdala for CBM versus placebo, which correlated with decreases in craving (DAQ) and arousal ratings |
| Wiers et al. (2015a) | *N* = 26 abstinent inpatients with AUD | 6 sessions<br>(3 weeks) of AAT-based CBM:<br>(1) *n* = 13 CBM alcohol push/pull (90%/10%)<br>(2) *n* = 15 Placebo alcohol push/pull (50/50)<br>(400 trials) | Implicit alcohol joystick AAT with alcohol and soft drink cues<br>(3 T fMRI) | - Pre-post behavioral bias: no significant interaction effect of group by time; no main effects of group; main effect of time at trend-level, with decreasing alcohol approach bias after training.<br>- Pre-post AAT BOLD response: mPFC activation for [(alcohol pull > alcohol push) > (soft drink pull > soft drink push)] decreased after CBM versus placebo, which correlated with decreases in behavioral bias scores in CBM group only |

non-anxious participants only (O'Toole and Dennis, 2012). Subjects were assigned to an "attention toward threat" ($N = 25$) or "away from threat" ($N = 24$) condition. CBM significantly changed attentional bias for threatening stimuli, but only for participants who showed attentional bias at baseline. CBM further affected early spatial attention in that the avoid threat training decreased P1 amplitudes to all faces; which, interestingly is an effect contrary to that found by Eldar and Bar-Haim (2010), possibly due to differences in experimental design. This may also suggest that CBM modifies attention biases differently in anxious than non-anxious individuals.

Third, a study with non-anxious females who were randomly assigned to CBM (toward threat) or 50/50 threat/neutral placebo training, CBM subjects showed increased P2 amplitudes associated with attention toward threat compared to placebo (Suway et al., 2013), which was in line with Eldar and Bar-Haim (2010). The CBM toward threat group also showed increased depression vulnerability, which suggests a direct effect of CBM on both behavior and brain.

These ERP results provide rich information with high temporal resolution about neural changes associated with the trained bias toward threat. That is, a single session of CBM enhanced early attentional processing N2 (Eldar and Bar-Haim, 2010) and P2 components (Suway et al., 2013), whereas it reduced later components P2 and P3 associated with more complex processing (Eldar and Bar-Haim, 2010) - but see also a decrease of the early component P1 in O'Toole and Dennis (2012). ERP analyses are thus sensitive to rapid cognitive events in attentional bias tasks. However, they are limited in spatial resolution, which is an advantage of fMRI.

*fMRI*

The first combined CBM/fMRI experiment assigned 29 healthy subjects to a 100% avoid threatening/negative words CBM ($n = 15$) or 100% attend threat ($n = 14$) (Browning et al., 2010), which is a training that replicated the procedure of MacLeod et al. (2002). After training, both groups performed a modified Pessoa task (Pessoa et al., 2005), in which fearful and neutral faces are presented while in a 3 T MRI scanner and participants perform a task requiring them to either attend or ignore the faces. As expected, participants in the avoid threat CBM decreased their attentional bias for fearful faces, whereas the group attending threat increased attentional biases. On a neural level, both training groups showed greater lateral PFC activation when the direction of attention was opposite of the training they received (i.e., opposite to behavioral rules learned at CBM), suggesting that CBM may modulate prefrontal regulation over anxiety. Further, there was enhanced connectivity between the identified lateral PFC clusters and visual association cortex, suggesting that the PFC was influencing selective attention to faces (Vuilleumier, 2005). As such, CBM may influence attention through modulation of the prefrontal cortex.

Taylor et al. (2014) were the first to combine CBM with fMRI in participants with high social anxiety. They examined the neural effects of a single session of CBM on brain reactivity to emotional faces in $N = 14$ participants (10 women) with scores > 40 on the Liebowitz Social Anxiety Scale (LSAS) (range 0–144; Fresco et al., 2001). A single session of Dot-Probe-based CBM with an 80% neutral-threat condition and 20% neutral-neutral (360 trials in total) was done while lying in a 3 T scanner. Before and after training, participants underwent the Emotion Face Assessment Task (Hariri et al., 2002). The main results revealed that for the main contrast of interest "faces versus shapes", activation in the amygdala, insula and the mPFC (subgenual ACC) decreased after training, whereas activity in the mPFC increased for this contrast. Correlations with behavioral measures showed that, first, decreased amygdala activation was associated with attenuated anxiety reactivity in response to an anxiety speech task, suggesting that CBM decreases anxiety reactivity through the amygdala. Decreased amygdalar and insular activation has been previously shown for psychotherapy treatment (Holzschneider and Mulert, 2011), and pharmacological treatment with benzodiazepines (Paulus et al., 2005) or SSRIs (Windischberger et al., 2010), suggesting similar effects as CBM in decreasing anxiety symptoms. Second, the enhanced mPFC activation after training was negatively associated with attentional allocation for threat and positively with anxiety reactivity to the stressor. The authors suggest that increased mPFC activation may reflect increased attentional control mechanisms over emotional processes (Taylor et al., 2014). Although the main limitations of the study are its small sample size and the lack of control group (i.e., neither a group without anxious symptoms nor a sham training control group in the same populations), these results suggest attenuation of amygdalar and insular reactivity to an emotional faces task as well as increased mPFC activation possibly involved in cognitive control.

Mansson and colleagues performed a series of studies on the effects of internet-delivered Dot Probe-based attentional CBM on neural processes utilizing fMRI in participants with social anxiety disorder (SAD). Internet-based trainings have been criticized for being less effective than lab-based studies (Linetzky et al., 2015), and the results of these studies may therefore be seen as exploratory. First, 4 weeks of Dot-probe based CBM in 11 participants with Social Anxiety Disorder (SAD) surprisingly increased amygdalar activation for emotional versus neutral faces on the affective face processing task (Hariri et al., 2002), whereas reversed patterns were shown for a CBT "control" group (Mansson et al., 2013). Second, dACC and amygdala activation on a self-criticism fMRI task predicted CBM treatment response 1 year later: responders (12/23 = 52%, according to a clinical improvement scale) showed lower dACC and amygdala activation for self > other-referred criticism as well as reduced dACC-amygdala coupling for the same contrast (Mansson et al., 2015). These two studies suggest a role of the dACC-amygdala coupling in response to and predicting effects of CBM. The main limitation of these two studies is that there is no good control group for CBM and that the combination of CBM and CBT makes it difficult to disentangle individual explanatory variance of each treatment. A healthy control group was introduced in the third, most recent study of Mansson et al. (2016), but the study surprisingly fails to provide a direct comparison between controls and SAD for the effects of CBM, as the main interaction of interest was involving the treatment interaction of training (CBM × CBT) on neural processes. Thirteen participants with SAD and 13 healthy controls performed 8 sessions of internet-delivered CBM. An additional 26 participants (13 SAD, 13 controls) underwent CBT, which was introduced in the study as an extra control group to CBM. The figures show that there is a tendency of CBM increasing amygdala volume and activation, but statistics are missing which makes it impossible to test whether CBM had effects on structural and functional measures. Statistics on whether a change in behavioral attentional bias was achieved were also missing. The study nevertheless concludes that CBT may have stronger effects on neural responsiveness in the amygdala than CBM (Mansson et al., 2016).

Last, a neatly controlled study by Britton et al. (2015) tested 30 healthy controls with high social anxiety scores on the LSAS (Fresco et al., 2001); a group comparable to Taylor et al. (2014). Participants were randomly assigned to a Dot Probe training away from threatening stimuli in 100% of cases ($N = 15$) or a 50/50 placebo training, with 8 sessions each. Before and after training, patients performed a Dot Probe task with angry and neutral faces while being in 3 T MRI; the second MRI was directly after an additional "acute" CBM in the scanner. ROI analyses were used to study fronto-amygdala activations on the Dot Probe Task. CBM decreased social anxiety symptoms as well as bilateral amygdala activation for the contrast (threat incongruent > congruent), as compared to placebo training. For both groups, threat-related activation in the amygdala at baseline was a predictor of social anxiety reductions.

In summary, these studies in anxiety show (1) effects of CBM on top down control processes in emotional processing (i.e., CBM "avoid threat" decreased P2 and P3 and lateral PFC activation; Eldar and Bar-Haim, 2010; Browning et al., 2010; CBM toward threat increased P2; Suway et al., 2013) (2) involvement in early attention processes (i.e.,

CBM "avoid threat" decreased P1; O'Toole and Dennis, 2012) and (3) involvement in reductions of bottom-up emotional processes encoded in the amygdala (CBM "avoid threat" decreased amygdala activation for threatening stimuli; Britton et al., 2015, Taylor et al., 2014; but see increased amygdala activation after internet-based CBM in a small internet-based study with patients with SAD without a control group in Mansson et al., 2013).

*Neural effects of retraining depressive behavior*

Similarly to anxiety, depression is characterized by selective attention for negative information, which may contribute to the preservation of depressive symptoms. There are currently two published studies investigating the neural effects of CBM in participants with depressive symptoms.

First, Beevers et al. (2015) studied the effects of CBM in adult patients with Major Depressive Disorder (MDD), who were randomly assigned to 4 weeks of CBM aiming to reduce negative attention bias ($N$ = 24: 85% dot away from dysphoric images) or 4 weeks of placebo attention training (probe with dysphoric or neutral images at equal probability). As expected, CBM reduced negative bias compared to placebo training, and in the CBM group only pre-post change in attention bias was correlated with change in depression symptoms. There was, however, no effect of group on depressive symptom reductions after training. CBM increased resting state functional connectivity between middle frontal gyrus and dACC versus placebo, a circuit that supports control over emotional information. Additional exploratory results show that for placebo, pre-post changes in connectivity in precuneus and medial frontal gyrus (circuit involved in sustaining attention to visual information) contributed to symptom improvement. These findings suggest that CBM may improve control over biased attention to negative information, and that deficits in general attentional control may also maintain depression symptoms, as evidenced by resting state connectivity and depression symptom improvement in the placebo training condition.

A recent study by Li et al. (2016) tested the neural effects of a Dot-probe based CBM with positive, neutral and negative faces in 41 young women with subthreshold depression as defined by a score > 14 on the Beck's Depression Index (BDI; Beck et al., 1996). Participants were randomly assigned to CBM with 87.5% of trials training toward positive cues ($n$ = 24) or placebo training toward negative/positive stimuli with a 50/50 ratio ($n$ = 17). Resting state scans were performed pre and post training in both groups. An additional non-depressed control group also performed resting state before training only. As hypothesized, CBM decreased depressive symptoms and increased attentional bias for positive stimuli. CBM also reduced the amplitude of low-frequency fluctuations of the right insula and right middle frontal gyrus; which showed greater fluctuations than in non-depressed subjects. Last, functional connectivity decreased between right insula and fronto-insular and supramarginal gyrus pre-post CBM training, which was associated with improvement of depressive symptoms. The results suggest that attentional CBM has the potential to normalize spontaneous brain activity in neural circuits that are involved in depression.

Altogether, these two studies show that CBM training to avoid dysphoric stimuli may increase connectivity in frontal regions (Beevers et al., 2015), but decrease connectivity between frontal areas and the insula (Li et al., 2016).

*Neural effects of CBM in addiction*

Studies on the neural effects of CBM in addiction so far have been limited to inpatients with AUD and to training on the implicit joystick-based AAT. More work has been performed on neural effects of goal-directed interventions, inhibition training, and other cognitive interventions in addiction, which has been recently reviewed elsewhere (Cabrera et al., 2016; Verdejo-Garcia, 2016; Zilverstand et al., 2016).

Wiers et al. (2015b) investigated the effects of 3 weeks of implicit joystick-based AAT CBM on a neural alcohol cue reactivity task. Thirty-two recently abstinent patients with AUD underwent six sessions of CBM for 3 weeks in which they pushed and pulled pictures of alcoholic and soft drink beverages according to the format of the picture (indirect task instruction). Patients were randomly assigned to a CBM training group that pushed away 90% of alcohol cues and 10% of soft drink cues ($N$ = 15), or a placebo training group for which the push/pull ratio of alcohol and soft drink cues 50/50 ($N$ = 17). Before and after training, patients performed a blocked design cue reactivity task in which they passively viewed alcohol and soft drink cues in a 3 Tesla MRI scanner. Cues used for MRI were different than cues during training, so results can be generalized to stimuli categories. Patients also rated alcohol craving before and after training using the Desire for Alcohol Questionnaire (DAQ; Love et al., 1998). Before training alcohol versus soft drink cues induced activation in the bilateral amygdala and NAcc over all participants. CBM more strongly reduced alcohol-cue induced bilateral amygdala activation and arousal ratings of alcohol cues, as compared to placebo training. There was a main effect of time for DAQ craving, but only in the CBM group reductions in amygdala activations were associated with reductions in alcohol craving. Reductions of cue-induced reactivity in the amygdala may therefore be an important mechanism of the therapeutic effectiveness of CBM in AUD. The authors could, however, not find a behavioral effect of CBM on the automatic approach bias scores, but suggest that imaging methods may be more sensitive to capture effects of CBM than behavioral measures. Moreover, as the authors note in the supplementary material, neither training type, nor baseline cue reactivity, or pre-post cue reactivity changes predicted relapse after 1 year of abstinence (Wiers et al. 2015b). Decreased relapse 1 year after CBM training was found in previous clinical studies that tested hundreds of inpatients with AUD (Eberl et al., 2013; Wiers et al., 2011), suggesting that the negative finding regarding clinical effects was due to suboptimal statistical power.

From 32 patients who performed pre-post cue reactivity, 26 patients also performed the AAT offline and in MRI, both before and after training (Wiers et al. 2015a). Before training, patients showed increased activation in the mPFC for the alcohol approach bias contrast [(alcohol pull > alcohol push) > (soft drink pull > soft drink push)], which was also shown in previous publications in patients versus controls (Ernst et al., 2014; Wiers et al., 2014). This activation in mPFC reduced after CBM training compared to placebo, and correlated with reductions in approach bias scores in the CBM group only. There were, however, no significant effects of CBM of behavioral approach bias. The results suggest that CBM affects mPFC activation involved in the automatic alcohol approach bias, which may be important for the clinical effectiveness of CBM. Although hypothesized, the nucleus accumbens was not affected by CBM training in these two studies.

In summary, the two CBM studies in addiction suggest that CBM decreases activation of the mPFC and amygdala in alcoholism, structures involved in motivational salience of cues and craving. The mPFC and amygdala were also involved in the alcohol approach bias in patients with AUD before training, compared to healthy controls (Ernst et al., 2014; Wiers et al., 2014).

## An integrative summary of findings

Overall, the first studies on neural effects of CBM that are discussed in this review provide preliminary evidence for CBM influencing both top-down and bottom-up processes in anxiety, depression and addiction. It has to be noted, however, that the studies are diverse in study design (e.g., different training and neuroimaging assessment tasks, single and multiple training sessions, clinical and non-clinical populations) and include methodological problems (e.g., no control groups;

Mansson et al., 2013; Taylor et al., 2014), lack of baseline scan (Browning et al., 2010) and small sample sizes that reduces statistical power (Britton et al., 2015; Wiers et al. 2015b), which makes it difficult to make strong conclusions on neural findings.

First, CBM showed enhancement of top down control processes involved in emotional processing in both anxious and non-anxious populations. That is, CBM "avoid threat" decreased ERP components P2 and P3 on a Dot Probe task (Eldar and Bar-Haim, 2010), whereas the reverse CBM training "toward threat" increased P2 amplitudes (Suway et al., 2013). Nevertheless, CBM "avoid threat" decreased P1 (O'Toole and Dennis, 2012), suggesting that CBM also affects more automatic early attention processes rather than top down control. The fMRI results of Browning et al. (2010) also suggest that CBM modulates prefrontal regulation over attention and anxiety. In this study, CBM training "avoid threat" or "toward threat" in healthy subjects resulted in opposing PFC activations on a Pesssoa task: lateral PFC activation was greater when the direction of attention on the Dot Probe Task was opposite of the type of CBM training they received (Browning et al., 2010). Two internet-based studies showed that patients with SAD who were responders to CBM treatment had reduced dACC activation and dACC-amygdala connectivity for self-criticism before training, compared to non-responders (Mansson et al., 2015), but that there were no direct effects of CBM in SAD patients on the same self-criticism task (Mansson et al., 2016). These studies partly support a role of the dACC-amygdala coupling in response to and predicting effects of CBM in anxiety. However, these studies suffer from methodological shortcomings (i.e., no good control groups, small sample sizes, internet-based, missing statistics for CBM contrasts in Mansson et al., 2016). For depressive behavior, two studies showed that CBM avoiding dysphoric stimuli increased resting state connectivity in frontal regions, which is also in line with the hypothesis that CBM may increase top-down control over emotional processing (Beevers et al., 2015). Li et al. (2016) showed decreases in connectivity between frontal areas and the insula for depression, which was associated with improvement of depressive symptoms. For the two studies in addiction, no evidence was found for increases in cognitive control mechanisms. Both studies suggest that CBM has the potential of normalizing functional connectivity in depression, but evidence remains exploratory, especially in view of the so far rather weak behavioral evidence for effects of CBM in depression.

Second, there is also evidence for CBM reducing bottom-up emotional processes. That is, CBM "avoid threat" decreased amygdala activation for threat cues on a Dot probe task (Britton et al., 2015; greater baseline amygdala activation predicted social anxiety symptoms reductions) and an emotional faces processing task (Taylor et al., 2014). The latter study also found reductions in insula and ACC activation for emotional versus neutral faces (Taylor et al., 2014). Surprisingly, however, the small internet-based CBM intervention in patients with SAD showed increased amygdala reactivity after CBM (Mansson et al., 2013). While the results of Taylor et al. (2014) suggest attenuation of amygdalar and insular reactivity to an emotional task as well as increased cognitive control, the findings of Mansson et al. (2013) are contrary to this hypothesis, but the latter study was confounded as the study was internet-based (Linetzky et al., 2015) and that there was no good control group. Interestingly, the two addiction studies also suggest that CBM reduces bottom-up motivational salience in the amygdala and mPFC on a basic cue reactivity task in patients with AUD, which was associated with craving and approach bias scores respectively (Wiers et al. 2015a, 2015b). These findings suggest that CBM decreases salience of alcohol cues encoded in the amygdala (Mahler and Berridge, 2009, 2012; Wiers et al., 2013c) and value of alcohol as a reward encoded in the mPFC (Ernst et al., 2014; Hare et al., 2009; Wiers et al., 2014).). Although this mechanism could play a role in the earlier reported clinical effects (Wiers et al., 2011; Eberl et al., 2013), it should be noted that these clinical effects were not replicated in the much smaller fMRI sample, probably due to lack of statistical power. Therefore, the current status of this neural mechanism underlying clinical effects remains hypothetical, and should be confirmed in a larger sample, ideally with mediation analysis (as has been demonstrated for the behavioral change in approach bias for alcohol, Eberl et al., 2013, and for alcohol-avoidance associations, Gladwin et al., 2015, but in much larger samples).

Despite the suggested role of CBM in reducing amygdala reactivity in bottom-up saliency processes, it should be noted that the reduction of amygdala activation may also be the effect of top-down biasing (Cunningham et al., 2008). Indeed, dACC and amygdala are strongly connected on tasks involving emotional conflicts (Etkin et al., 2006), making it challenging if not impossible to disentangle the specific roles of bottom-up versus top-down responses (Gladwin et al., 2011). Hence, the question whether the primary neural mechanism in CBM is a change in bottom-up reactivity or in top-down biasing may be an oversimplification, given their intertwined nature.

## Limitations and future directions

There are several limitations to the reviewed studies on neural effects of CBM. The most important limitation is that all studies discussed have small sample sizes (e.g., some report on $n = 15$ or lower per training group; Britton et al., 2015; Wiers et al. 2015a; Wiers et al. 2015b). Although neural effects of behavioral therapy have been previously reported in groups of around 15 patients (e.g., Vollstadt-Klein et al., 2011), many of the neuroimaging results reported here cannot replicate behavioral effects of CBM that were shown in larger samples of $N = 200$ (Wiers et al., 2011). Therefore, replication of initial imaging findings in larger groups is necessary to draw conclusions on neural effects of CBM.

Another shortcoming of the reviewed studies is that they are diverse in study design, which makes it difficult to integrate results of different studies. First, training and imaging tasks of the 13 studies were very different in nature. That is, most CBM studies in anxiety and depression used the Dot probe task with EEG and fMRI to capture neural effects of training (Beevers et al., 2015; Britton et al., 2015; Eldar and Bar-Haim, 2010; O'Toole and Dennis, 2012; Suway et al., 2013), whereas the other fMRI training studies reviewed here used different tasks: an affective face processing task (Mansson et al., 2013), Pessoa task (Browning et al., 2010), emotional face task (Taylor et al., 2014), self-referential criticism task (Mansson et al., 2015; Mansson et al., 2016) and fMRI resting state plus a Dot probe task outside the scanner (Li et al., 2016). Since different neuroimaging tasks were used, it is important to differentiate how these tasks capture specific aspects of retrained attentional processes, as a function of the emotional content of stimuli. For example, the Dot Probe task presents neutral and fearful stimuli and trials are split by congruency; i.e., the position of the probe. Although the outcome contrast is interpreted as measuring the neural processes underlying retrained attention, it may likely measure the subsequent response of the system when the probe is consistent or inconsistent with the initial biasing process, especially since all CBM trainings were Dot Probe-based. Therefore, tasks that are more independent of the CBM training task, such as the Pessoa task, emotional face task and self-referential criticism task, may be more optimal in measuring treatment responses that can be inferred to generalize to more general emotional processes. For example, the study of Browning et al. (2010) used a Pessoa tasks that allows for a dissociation for emotional and attentional processes that is independent of the Dot Probe task. They found greater PFC activation for incongruent trials, suggesting that CBM may increase cognitive control over anxiety (Browning et al., 2010). For addiction, neural effects of the AAT-based CBM was captured using either the AAT with MRI (Wiers et al. 2015a) and a basic blocked-design alcohol cue reactivity task (Wiers et al. 2015b) and showed different outcomes. While CBM decreased mPFC activation on the AAT, it decreased amygdala activation on a passive viewing alcohol cue reactivity task. Also here, mPFC

activation may have been confounded with the training on AAT itself. It may have been less rewarding to do a training-incongruent movement of pulling alcohol cues. It should be noted that the AAT-training effects were also found to generalize to a verbal categorization task, the implicit association task (IAT, Wiers et al., 2011, and changed alcohol-avoidance associations were found to mediate the clinical effect (Gladwin et al., 2015). Future studies should take these task specifics into consideration.

Second, training included different schemes with single or multiple sessions. Most studies in anxiety consisted of single session CBM and studied its immediate effect on EEG or fMRI paradigms (see Table 1), but see Britton et al. (2015) and the internet-based studies of Mansson et al. (2013, 2015, 2016) that used a 4-week CBM training paradigm with 8 sessions in patients with SAD or social anxiety symptoms. The depression and substance use disorder studies used training paradigms over 4 and 3 weeks respectively (see Table 1). Although investigation into how many sessions are needed for an optimal clinical effect exist (e.g., Eberl et al. (2014) show that 6 CBM sessions are optimal in reducing relapse in alcoholism), it remains unknown what optimal CBM training paradigms are for neural outcome measures. This is important, however, as neural changes after multiple CBM sessions may be due to the CBM itself or, indirectly, due to changes in behavioral symptoms. This problem may be reduced if the neural effects of CBM are assessed before changes in symptoms have occurred.

Further methodological weaknesses of the reviewed studies were that some did not include a control group (e.g., Mansson et al., 2013; Taylor et al., 2014) or a baseline scan (Browning et al., 2010). Therefore, the main directions for future research are that (1) sample sizes need to be larger to reach adequate power, (2) CBM studies need to include control groups, (3) all studies have been exploratory in nature and future studies with larger sample size are needed to do a-priori hypotheses testing, with pre-registered outcomes and analysis strategies, and (4) congruence on task and training design may make it possible to replicate findings or better compare results from different studies, potentially using meta-analyses software such as Brainmap (Eickhoff et al., 2009). These future directions are particularly important given the recent focus on unreliability and lack of reproducibility of psychological and neuroscientific findings (Open Science, 2015).

Additional suggestions for future research on neural processes and CBM include measuring the neural mechanisms of training itself. Since CBM was performed while lying in the scanner in the designs of Taylor et al. (2014) and Britton et al. (2015), a unique measure would have been the responses to Dot Probe stimuli. In line with this, variance-based temporal dynamic measures of automatic biases could be considered (e.g., Zvielli et al., 2015) and related to neural processing. Further, internet-based CBM, as was discussed in the studies of Mansson et al. (2013, 2015, 2016) may be a potentially interesting for future large-scale CBM training. A drawback is, however, that the efficacy of online training may not be as strong as offline studies, and negative results of internet-based CBM have been reported for anxiety research (which generally also show weaker behavioral effects; Linetzky et al., 2015), as well as for addiction (Wiers et al., 2015c), compared with more positive effects in a clinical setting. The stronger effects of CBM delivered in clinic versus online settings could clarify if comparisons of delivering CBM in these two settings controlled for factors such as number and duration of training sessions, and distraction. It has been argued that in addiction it may be crucial to motivate participants to change their behavior before training; either in a clinical setting or online (Boffo et al., 2015; van Deursen et al., 2013). In anxiety, there is preliminary evidence that inducing the right state before training (some level of anxiety) might yield better effects, and this could also improve efficacy of training online (Kuckertz et al., 2014).

A line of research that may benefit from the findings discussed in this study is the enhancement of training using stimulation of the lateral PFC utilizing transcranial direct current stimulation (Gladwin et al., 2016). This technique has been shown to be successful in the enhancement of working memory including selective attention (Gladwin et al., 2012; Ohn et al., 2008) and has been shown to reduce craving for alcohol (e.g., den Uyl et al., 2015). Stimulation with tDCS may support executive functions that are necessary for successful inhibitions. Indeed, a recent study performed an attentional CBM using the Dot Probe task in combination with tDCS targeting the left dlPFC, which resulted in greater evidence of attentional bias acquisition in the targeted direction (either toward or away from threat) compared with participants in a sham tDCS condition (Clarke et al., 2014a). This supports the hypothesis that increased activity in the lateral PFC is not simply a consequence of acquired attentional bias but directly contributes to the modification of the bias. This is consistent with the implications of neuroimaging research performed by Browning et al. who demonstrated greater activity in the lateral PFC after CBM. An interesting future study may be to study behavioral as well as neural effects of tDCS, which may contribute largely to the understanding of the neural effectiveness of CBM.

## Conclusion

From the first 13 studies on CBM and neuroimaging, it becomes clear that CBM has the potential of changing neural processes involved in the neuropathology of anxiety, depression and addiction. These studies suggest a role of the fronto-amygdalar circuitry in the efficacy of CBM in anxiety and addiction, and effects on connectivity between frontal gyrus, anterior cingulate and insula in depressive behavior. The reviewed findings are of clinical importance as they may provide insight into target regions for neuromodulatory techniques such as tDCS.

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