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DOI
10.1111/adb.12221

Publication date
2015

Document Version
Final published version

Published in
Addiction Biology

Addiction Biology

SSA SOCIETY FOR THE STUDY OF ADDICTION

HUMAN NEUROIMAGING STUDY

doi:10.1111/adb.12221

Effects of cognitive bias modification training on neural signatures of alcohol approach tendencies in male alcohol-dependent patients

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ABSTRACT

Alcohol-dependent patients have been shown to faster approach than avoid alcohol stimuli on the Approach Avoidance Task (AAT). This so-called alcohol approach bias has been associated with increased brain activation in the medial prefrontal cortex and nucleus accumbens. Cognitive bias modification (CBM) has been used to retrain the approach bias with the clinically relevant effect of decreasing relapse rates one year later. The effects of CBM on neural signatures of approach/avoidance tendencies remain hitherto unknown. In a double-blind placebo-controlled design, 26 alcohol-dependent in-patients were assigned to a CBM or a placebo training group. Both groups performed the AAT for three weeks: in CBM training, patients pushed away 90 percent of alcohol cues; this rate was 50 percent in placebo training. Before and after training, patients performed the AAT offline, and in a 3 T magnetic resonance imaging scanner. The relevant neuroimaging contrast for the alcohol approach bias was the difference between approaching versus avoiding alcohol cues relative to soft drink cues: [(alcohol pull > alcohol push) > (soft drink pull > soft drink push)]. Before training, both groups showed significant alcohol approach bias-related activation in the medial prefrontal cortex. After training, patients in the CBM group showed stronger reductions in medial prefrontal cortex activation compared with the placebo group. Moreover, these reductions correlated with reductions in approach bias scores in the CBM group only. This suggests that CBM affects neural mechanisms involved in the automatic alcohol approach bias, which may be important for the clinical effectiveness of CBM.

Keywords Addiction, alcohol dependence, approach bias, cognitive bias modification training, medial prefrontal cortex.

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INTRODUCTION

A central paradox in addictive behavior is the continuation of drug use despite negative consequences and high rates of relapse after attempts to abstain (Stacy & Wiers 2010). There are several theories that attempt to explain addictive behavior and its persistence. For example, individuals may have a predisposition to be insensitive to natural rewards (i.e. reward-deficiency model) leading to drug taking as a way to compensate for this (Blum *et al.* 2012; Limbrick-Oldfield, van Holst & Clark 2013), they may experience negative states that underlie withdrawal (Koob & Le Moal 2001), be generally poor in inhibiting control over drug-taking behavior (Jentsch & Taylor 1999; Volkow *et al.* 2002; Goldstein & Volkow 2011), or their drug-associated neuroadaptations in reward

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learning may bias behavior towards drug taking (Heinz *et al.* 2011). Dual process models of addiction propose a conflict between two qualitatively different types of processes that underlie the paradoxical behavior typical for addiction: automatic or impulsive processes that cause a strong motivational tendency to approach drugs (after repeated use) and reflective processes that may motivate to refrain from drugs for long-term reasons (Carter & Tiffany 1999; Bechara 2005; Wiers *et al.* 2007). Besides the drug itself, cues that are associated with drugs increase in salience over the course of repetitive drug taking, and could act as a motivational magnet (Robinson & Berridge 1993, 2003), or trigger the habitual process of drug taking (Robbins & Everitt 1999; Everitt & Robbins 2005). Approach and avoidance processes have been hypothesized to operate largely outside of conscious awareness and may lead to drug craving and relapse, even after years of abstinence (Heinz *et al.* 2009).

Alcohol approach/avoidance inclinations can be measured with explicit self-reports (e.g. Barkby *et al.* 2012; McEvoy *et al.* 2004) or with implicit indirect tasks such as the Approach Avoidance Task (AAT). In the AAT, participants push and pull pictorial cues with a joystick in response to a content-irrelevant format of the cue (e.g. landscape or portrait). Alcohol-dependent patients have been shown to faster pull than push alcohol cues (Wiers *et al.* 2011), also compared with soft drink cues (i.e. 'alcohol approach bias'; Ernst *et al.* 2014; Wiers *et al.* 2014b). The approach bias has been associated with drug craving (Wiers *et al.* 2013) and with increased reward-related brain activations in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc) (Ernst *et al.* 2014; Wiers *et al.* 2014b). Increased reactivity to alcohol cues in these areas has been shown to be fundamental in the pathology of alcohol dependence because this measure often correlates with craving and predicts relapse (Grusser *et al.* 2004; Myrick *et al.* 2008; Heinz *et al.* 2009; Koob & Volkow 2010; Schacht, Anton & Myrick 2013).

Although approach tendencies towards drugs were thought to be rather permanent and hence serve a causal role in craving and relapse (Robinson & Berridge 1993, 2003), it has been shown that the approach bias can be modified by means of a form of cognitive bias modification (CBM). This training scheme relies on performing a modified AAT, in which alcohol cues are avoided in 90 percent of the trials and approached in the remaining 10 percent. In a heavy drinking student population, one session of CBM led to a reduction in the alcohol approach bias and a reduction in alcohol intake in a beer tasting test after training (Wiers *et al.* 2010). Subsequently, in two clinical trials, six sessions of CBM over three weeks reduced approach bias as well as relapse rates after abstinence in alcohol-dependent patients (Wiers *et al.* 2011; Eberl *et al.* 2013), showing the therapeutic potential of CBM. Moreover, in a recent study, CBM decreased amygdala reactivity while passively viewing alcohol cues, which was associated with reductions in alcohol craving (Wiers *et al.* 2014a). However, the effects of CBM on neural approach/avoidance tendencies remain hitherto unknown. Insight in the neural effects of CBM on approach tendencies is important for a better understanding of the working mechanisms underlying CBM and its clinical impact.

Here, we studied the effects of CBM on behavioral approach/avoidance tendencies and their neural signatures in alcohol-dependent patients. In a double-blind placebo-controlled design, patients were randomly assigned to a CBM training group or a placebo training group and performed the respective training for three weeks. The CBM training group pushed away 90 percent of alcohol cues whereas this rate was 50 percent in the placebo training group. Before and after training, patients performed the AAT, both offline, to measure approach bias, as well as in a 3 T magnetic resonance imaging (MRI) scanner to measure neural activation. Moreover, patients filled out self-report questionnaires on alcohol approach/avoidance inclinations and craving. We hypothesized that the behavioral approach bias, self-report measures and approach bias-related activations in the mPFC and NAcc would decrease after training in CBM versus placebo. In addition, changes in neural activation were expected to covary with changes in automatic and self-reported approach/avoidance behavior, and with craving.

MATERIALS AND METHODS

Subjects

Thirty-six male alcohol-dependent in-patients were recruited from the Salus Clinic, Lindow, Germany. Exclusion criteria for all patients were a history of neurological dysfunctions, Axis I psychiatric disorders according to DSM-IV criteria other than alcohol or nicotine dependence (M.I.N.I. plus interview; Sheehan *et al.* 1998), being abstinent from alcohol more than 4 months before participation, and intake of psychoactive medication, as tested by urine drug screening by clinic entrance. Patients were free from psychoactive medication or other drugs at least six months before participation. The Ethical Committee of the Charité, Universitätsmedizin Berlin approved the study, and after complete description of the study to the subjects written informed consent was obtained. Pre-training neuroimaging data of the first 20 patients have been reported previously in Wiers *et al.* (2014b) and effects of CBM on a passive alcohol cue reactivity task have been reported in Wiers *et al.* (2014a).

Table 1 Demographic and clinical data of participants in the CBM and placebo training group.

	CBM		*Placebo*		
Characteristic	*Mean*	*SD*	*Mean*	*SD*	P-*value*
Age, years	45.23	7.03	42.62	8.66	0.41
Years of education	10.46	1.39	10.54	1.51	0.89
Wechsler Adult Intelligence Scale	15.46	5.40	13.54	5.21	0.36
Length of abstinence, days	36.23	25.84	55.23	38.89	0.16
Duration of dependence, years	18.69	9.75	13.08	7.87	0.12
Alcohol intake before admission, g/day	345.96	205.76	237.23	177.04	0.16
Alcohol Dependence Scale	18.31	9.88	14.50[a]	5.63	0.25
Trait anxiety	36.27[b]	8.00	34.36[b]	7.69	0.58
Cigarettes per day	18.62	10.56	17.73	8.23	0.81
Pack years	23.35	18.05	18.12	15.37	0.44
State anxiety	33.54	7.54	33.23	8.23	0.92

[a]$N = 12$. [b]$N = 11$. CBM = cognitive bias modification.

Patients were randomly assigned to a CBM or a placebo group. Patients were recruited within the first week of clinic entrance, and per week a maximum of four patients were included to the study. Because of practical reasons of training, all participants in one week were selected to be part of one training method (either training type '1' or '2') with one response type (either push landscape/pull portrait or pull landscape/push portrait pictures). There was no selection bias in time of clinic entrance. In the last weeks of the study, patients were assigned to groups while taking into consideration their age, years of education and drinking behavior, to aim for matched groups for these variables. Both the experimenter and the trainers were always blind to whether training 1 or 2 was CBM or placebo. This information was written on a sheet, which was open to the experimenter only after data collection. Two patients did not complete the training (one CBM, one placebo) and two patients were not able to show up at the second day of testing due to administrative reasons (both CBM). Four patients (two CBM, two placebo) had anatomical difficulties to fit in the narrow MRI scanner together with the joystick and were hence unable to perform the online AAT. Because the remaining participants with evaluable data (13 CBM versus 15 placebo) were not matched for length of abstinence before testing, two patients from the placebo group with the shortest duration of abstinence were excluded from our final analyses to compare groups matched for abstinence [1]. This left a total of $N = 13$ patients in CBM and $N = 13$ in placebo for final analyses, who were matched for demographic and clinical variables (see Table 1) and for number of smokers ($N = 11$ smokers in CBM and $N = 12$ smokers in placebo, $\chi^2 = 0.38$, $P = 0.54$). Smokers were abstinent from tobacco for at least 1.5 hours before scanning. The number of cigarettes per day as well as 'pack years' (i.e. [number of cigarettes/day years of smoking/20], with 20 as the number of cigarettes in a common pack) was acquired.

[1] An exploratory analysis revealed that our main neuroimaging result (signification interaction effect of time × group in the mPFC at $P < 0.005$ FWE) was not affected by the exclusion of these two patients.

Questionnaires

On the first day of testing, patients completed the Alcohol Dependence Scale (Skinner & Allen 1982), the Matrix Reasoning of the Wechsler Adult Intelligence Scale as a proxy for general intelligence (Kaufman & Lichtenberger 2006), and the Spielberger State-Trait Anxiety Questionnaire (STAI) to evaluate state and trait anxiety (Spielberger *et al.* 1983).

On both days, alcohol craving was assessed with the Desire for Alcohol Questionnaire (DAQ; Love, James & Willner 1998) and self-reported alcohol approach behavior was assessed with the Alcohol Approach Avoidance Questionnaire (AAAQ; McEvoy *et al.* 2004). The AAAQ has three scales (obsessed/compelled, inclined/indulgent, resolved/regulated) reflecting intense approach inclinations, mild approach inclinations and avoidance inclinations, respectively.

Experimental tasks at pretest and post-test

Behavioral AAT

The zoom version of the AAT was used to measure the offline behavioral alcohol approach bias (Rinck & Becker 2007). Participants pushed and pulled via a joystick (Logitech attack 3) in response to the format of the cue (landscape or portrait) and had to respond to a cue within two seconds. Pulling and pushing the joystick increased and decreased the size of the cue, respectively. In both pre- and post-assessment AAT, 20 practice trials were

followed by 80 test trials, presented over two blocks. Picture format to response assignment was counterbalanced: half of the participants pulled landscape and pushed portrait cues, and vice versa. A set of 40 alcohol and 40 soft drink images was used and pictures were pushed and pulled in equal ratios (50/50) (Wiers *et al.* 2014a,b).

Functional MRI AAT

The functional MRI (fMRI) task was identical to the paradigm used in Wiers *et al.* (2014b) using the Fiber Optic Joystick (Current Designs Philadelphia, PA, USA). The 80 pictures used in the offline behavioral AAT were presented in an event-related design, with a total of 160 trials over four blocks, and pictures were pushed and pulled equally often (50 percent/50 percent). Moreover, the online AAT had the same zooming feature as the offline task (i.e. pushing and pulling cues were accompanied with the visual feedback of the cue zooming out and in, respectively). Participants had to respond to a picture within two seconds. When subjects made an error or reacted too slowly, a red cross appeared on the screen. Intertrial intervals were 4, 6 or 8 seconds, distributed hyperbolically and at random (Miezin *et al.* 2000). Participants received feedback on their accuracy rate after each of the four runs.

CBM training

The CBM training scheme was an adapted version of the AAT, as has been used in previous training studies (Wiers *et al.* 2011; Eberl *et al.* 2013; Wiers *et al.* 2014a). Both groups performed six training sessions over 3 weeks, each consisting of 400 trials (approximately 15 minutes). The experimental CBM group pushed away alcohol in 90 percent of the cases and pulled alcohol in 10 percent, whereas this rate was 50 percent for both drink types in the placebo group. Twenty cues were used for training (10 alcohol and 10 soft drink; Eberl *et al.* 2013; Wiers *et al.* 2011). To test for neural effects based on stimulus categories (alcohol and soft drink) rather than on specific pictures, we used different yet comparable cues (i.e. different pictures but of the same drinks) in the training and in the AAT assessments.

fMRI acquisition and preprocessing

Data were collected using a 3 T whole-body MRI scanner (MAGNETOM Trio, TIM-Technology; Siemens, Erlangen, Germany), 12-channel head coil, standard T2-weighted echo planar imaging (EPI) sequence, sequential descending acquisition, repetition time 2 seconds, echo time 25 milliseconds, flip angle $\alpha = 80°$, 64×64 pixels in-plane resolution, 34 slices, slice thickness 3 mm, voxel dimensions $3 \times 3 \times 3$ mm^3, a 0.75-mm gap between slides, field of view 192×192 mm^2. Data analysis was performed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK) with the following preprocessing procedure: spatial realignment, slice-time correction (reference slice = 17, acquired half-way through the repetition time) with normalization to the standard Montreal Neurological Institute (MNI) EPI template (final voxel size after normalization $3 \times 3 \times 3$ mm^3) and smoothing with an 8-mm full width at half maximum Gaussian kernel (Wiers *et al.* 2014b). Participants did not move more than 3 mm or 3° within runs. The details of fMRI acquisition and preprocessing were identical to those of a previous study (Wiers *et al.* 2014b).

Statistical analyses

Behavioral measures

For the AAT, response times (RTs) were computed per trial as the time required from the onset of stimulus presentation until the joystick reached a maximum (push) or minimum (pull) position. Responses that were missed or incorrect were discarded based on each participant's performance. Alcohol approach bias scores were calculated by subtracting median difference scores of push-pull trials of alcohol and soft drink cues ([alcohol push-pull]–[soft drink push-pull]). Positive alcohol approach bias scores indicate an alcohol approach bias (i.e. the tendency to faster pull than push alcohol cues, relative to soft drinks) whereas negative approach bias scores indicate an avoidance bias for alcohol (i.e. faster push than pull alcohol compared with soft drinks) (Wiers *et al.* 2014b).

Three 2×2 mixed ANOVAs on alcohol approach bias, and AAAQ and DAQ craving scores were calculated, with the within-subject factor time (pre- versus post-training) and the between-subject factor group (CBM versus placebo). *Post hoc* group comparisons were performed with paired *t*-tests and an alpha of 0.05. Effects with significance levels of $0.05 < P < 0.1$ are reported as trends. Behavioral data analysis and correlations with neural peak activations were carried out using SPSS 20 (IBM, Armonk, NY, USA).

fMRI data

There were four fMRI regressors for every subject: alcohol pull, alcohol push, soft drink pull, soft drink push. The regressors were defined as the interval between stimulus presentation and the maximum position (push or pull) of the joystick, with the trial's RT set as the duration of the events (≤2 seconds). Missed trials and the six realignment parameters were included as regressors of no interest. On the single subject level, the contrast of interest was ([alcohol pull > alcohol push] >[soft drink pull > soft drink push]). On the second level, a flexible factorial design was used including the first level contrast images, with time (pre and post), group (CBM/placebo) and

Table 2 Raw data on the Approach Avoidance Task before training and after training in both groups.

	CBM		*Placebo*		
Characteristic	*Mean*	*SD*	*Mean*	*SD*	P-*value*
Alcohol pull (pre)	861.6	150.9	870.4	174.6	0.89
Alcohol push (pre)	854.0	166.9	898.4	194.0	0.54
Soft drink pull (pre)	890.6	136.0	879.4	162.3	0.85
Soft drink push (pre)	912.0	167.3	861.8	147.5	0.43
Alcohol pull (post)	841.7	130.6	836.3	129.0	0.92
Alcohol push (post)	819.4	189.1	872.0	240.2	0.54
Soft drink pull (post)	837.5	138.8	844.8	163.6	0.90
Soft drink push (post)	829.0	123.5	822.8	108.5	0.89

CBM = cognitive bias modification.

subject constants as factors. *Post hoc t*-tests were used to explore directions of the interaction of time × group.

Based on our hypotheses, the mPFC and bilateral NAcc were chosen as regions of interest (ROIs) and were used for small-volume correction (SVC) of the results with a significance threshold of $P < 0.05$, family-wise error (FWE) corrected. ROIs were selected using the same procedure of Wiers *et al.* (2014b): the NAcc was defined by the anatomical WFU Pickatlas (Maldjian *et al.* 2003), and because the mPFC is anatomically not clearly defined (e.g. the WFU Pickatlas does not include an mPFC or vmPFC ROI), the mPFC ROI was downloaded from an atlas of functional ROIs (Shirer *et al.* 2012). Both ROIs have been used in our previous AAT study (Wiers *et al.* 2014b). Whole-brain analyses using a liberal threshold of $P < 0.005$ uncorrected are presented in supplementary materials. Coordinates are reported in MNI space and brain activations were labelled with the Anatomical Automatic Labeling atlas of XJview software for SPM8 (www.alivelearn.net/xjview8/).

Betas of the peak interaction effect of time × group of the approach bias contrast ([alcohol pull > alcohol push] > [soft drink pull > soft drink push]) were extracted per subject using SPM. These values were correlated (Pearson's *r*, using SPSS) with pre-post offline approach bias scores, AAAQ as well as DAQ craving scores, for each group separately. Task-related activations were correlated with offline approach bias scores (rather than those collected during fMRI measurement) to ensure independence of measures. That is, RTs on the fMRI AAT were already included in the imaging model as duration of separate events and hence could not be used for correlation purposes.

RESULTS

Behavioral effects of CBM training

Raw reaction times (RTs) and alcohol approach bias scores on the AAT, DAQ craving and explicit alcohol approach bias inclinations on the AAAQ pre-, post- and pre-post training were distributed normally in both groups (Kolmogorov–Smirnov test: all $P > 0.33$).

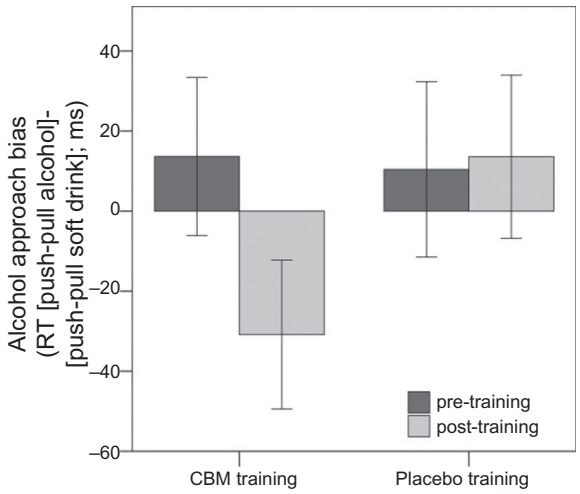

Figure 1 Alcohol approach bias scores before and after training in CBM and placebo. There were no significant interactions or main effects. Approach bias scores decreased as a trend in CBM ($P < 0.08$) but not in placebo. Error bars represent 1 SE of the mean

A 2 × 2 × 2 ANOVA of time × movement × group on raw AAT RTs demonstrated a trend for the main effect of time ($F_{1,24} = 3.71$, $P = 0.066$; with RTs decreasing over time, see Table 2) and of drink × group ($F_{1,24} = 3.18$, $P = 0.087$). There were no other main or interaction effects (all $P > 0.29$). Although the approach bias scores ([alcohol push-pull]–[soft drink push-pull]) were in the expected direction (see Fig. 1), there was neither an interaction effect of time × group ($F_{1,24} = 1.26$, $P = 0.27$) nor a main effect of time ($F_{1,24} = 0.95$, $P = 0.34$) or of group ($F_{1,24} = 1.17$, $P = 0.29$). Exploratory paired *t*-tests on approach bias scores demonstrated that while in CBM the approach bias scores decreased as a trend (bias pre = 13.65 ± 19.76 SE, bias post = –30.85 ± 18.61, $t_{12} = 1.92$, $P = 0.079$), they remained unchanged in the

placebo condition (bias pre = 10.42 ± 21.90 SE, bias post =13.58 ± 20.39, $t_{12} = -0.088$, $P = 0.93$) (see Fig. 1).

There was a trend-wise main effect of time on AAAQ sum scores ($F_{1,21} = 3.87$, $P = 0.063$), but not of group ($F_{1,21} = 0.20$, $P = 0.66$), and no interaction effect of time × group ($F_{1,21} = 0.64$, $P = 0.43$). Exploratory paired *t*-tests in both groups separately demonstrated that the main effect was due to the CBM group where AAAQ scores decreased at trend level (pre = 39.23 ± 4.34, post = 28.33 ± 4.72, $t_{11} = 2.12$, $P = 0.058$), whereas this was not the case in the placebo group (pre = 38.92 ± 5.73, post = 34.09 ± 3.54, $t_{10} = 0.77$, $P = 0.462$). The effects on the AAAQ were particularly apparent for the obsessive/compelled subscore of the AAAQ, which decreased in the CBM group (pre = 1.48 ± .32, post = 0.69 ± 0.20, $t_{11} = 3.62$, $P = 0.004$) but not in the placebo group (pre = 1.58 ± .61, post = 0.91 ± 0.31, Δ = 0.45 ± 1.65, $t_{10} = 0.91$, $P = 0.38$). There were no main or between-group effects for the two other subscores (inclined/indulgent and resolved/regulated; $P > 0.21$).

For DAQ craving scores, there was a main effect of time ($F_{1,23} = 6.5$, $P = 0.018$), but not of group ($F_{1,23} = 1.31$, $P = 0.27$), and no interaction effect of time × group ($F_{1,23} = 1.76$, $P = 0.20$). Exploratory paired *t*-test demonstrated that the main effect was due to the CBM group, where craving scores significantly decreased (pre = 16.38 ± 2.05, post =11.92 ± 10.85, $t_{11} = 4.03$, $P = 0.002$), whereas this was not the case in the placebo group (pre = 11.92 ± 5.01, post = 10.85 ± 3.76, $t_{12} = 0.72$, $P = 0.49$).

Effects of CBM on neural approach/avoidance activations

Before training, patients pooled over both groups showed significant alcohol approach bias-related activation in the mPFC (peak [x, y, z] = [−12, 47, 49], $t = 4.63$, $P = 0.05$ FWE SVC, middle frontal gyrus/Brodmann area [BA] 9), but not in the NAcc, not even at a more liberal threshold of $P < 0.005$ uncorrected. *Post hoc* contrasts revealed that the mPFC was activated in the contrast [alcohol pull > soft drink pull] (peak = [−6, 59, 7], $t = 5.26$, $P = 0.013$ FWE SVC, medial frontal gyrus), but not in the contrast [soft drink push > alcohol push], or in [alcohol pull > alcohol push] or [soft drink push > soft drink pull]. There were no group differences in mPFC activations before training. In line with our previous report (Wiers *et al*. 2014b), none of the behavioral measures correlated with the peak activation in the mPFC.

When comparing pre- with post-training, there was an interaction effect of time × group: the CBM group showed stronger reductions in mPFC activation compared with the placebo group (peaks are: [−21, 44, 7], $t = 8.15$, $P < 0.0001$ FWE SVC, dorsal anterior cingulate cortex (dACC)/BA32; [−27, 38, 40], $t = 6.06$, $P = 0.003$ FWE SVC, middle frontal gyrus/BA9; and [15, 44, 10], $t = 5.44$, $P = 0.011$ FWE SVC, dACC/BA32; see Fig. 2). *Post hoc t*-tests revealed that mPFC activation decreased in the CBM group (peak = [−18, 44, 7], $t = 5.46$, $P = 0.011$ FWE SVC), but not in the placebo group at $P < 0.05$ FWE and $P < 0.005$ uncorrected. In addition, exploratory *post hoc* contrasts showed that there was a significant interaction effect of time × group for the contrast [alcohol pull > soft drink pull]: the mPFC decreased in the CBM group versus the placebo group (peak= [−18, 44, 7], $t = 4.82$, $P = 0.041$ few), but also had increased mPFC activation for [alcohol push > soft drink push] (peak = [−21, 44, 37], $t = 9.05$, $P < 0.0001$ FWE) compared with placebo. There were no significant interactions for [alcohol pull > alcohol push], or for [soft drink push > soft drink pull] at $P < 0.05$ FWE. There was no interaction effect of time × group in the NAcc at $P < 0.05$ FWE, or at $P < 0.005$ uncorrected.

There was a main effect of time in both ROIs: activation in mPFC (peak = [9, 38, 13], $t = 7.10$, $P < 0.0001$ FWE SVC) and NAcc (peak left = [−9, 5, −8], $t = 3.27$, $P = 0.037$ FWE SVC; and only significant using a unilateral ROI, peak right = [12, 8, −5], $t = 2.71$, $P = 0.047$ FWE SVC) decreased over time. Supporting Information Table S1 in the supplementary material provides whole-brain training effects (main effects and interaction) on approach bias-related activations at $P < 0.005$ uncorrected, showing that the mPFC activations for the interaction of time × group are also present when correcting for the whole brain (peak = [−18, 44, 7], $t = 4.82$, $P = 0.001$ FWE). No other regions were activated in the whole-brain analysis using the stringent threshold of $\alpha = 0.05$ FWE.

Correlations with behavioral measures

Decreases in mPFC activations (i.e. the activated peak [−21, 44, 7] of the interaction effect of time × group on our contrast of interest [(alcohol pull > alcohol push) > (soft drink pull > soft drink push)]) correlated with pre-post training decreases of behavioral alcohol approach bias scores in the CBM group ($r = 0.797$, $P = 0.001$) but not in the placebo group ($r = -0.128$, $P = 6.78$) (Fig. 3). Moreover, pre-post peak activation in the mPFC correlated with pre-post AAAQ sum scores in the CBM group ($r = 0.592$, $P = 0.042$, $N = 12$), but not in the placebo group ($P = 0.21$, $N = 11$).

Activations in mPFC did not correlate with decreases in DAQ craving in either group (both $P > 0.78$). In addition, decreases in the three behavioral measures (alcohol approach bias, AAAQ and DAQ scores) did not correlate with each other in either group ($P > 0.14$).

Baseline mPFC activation in our main alcohol approach bias contrast before training did not correlate

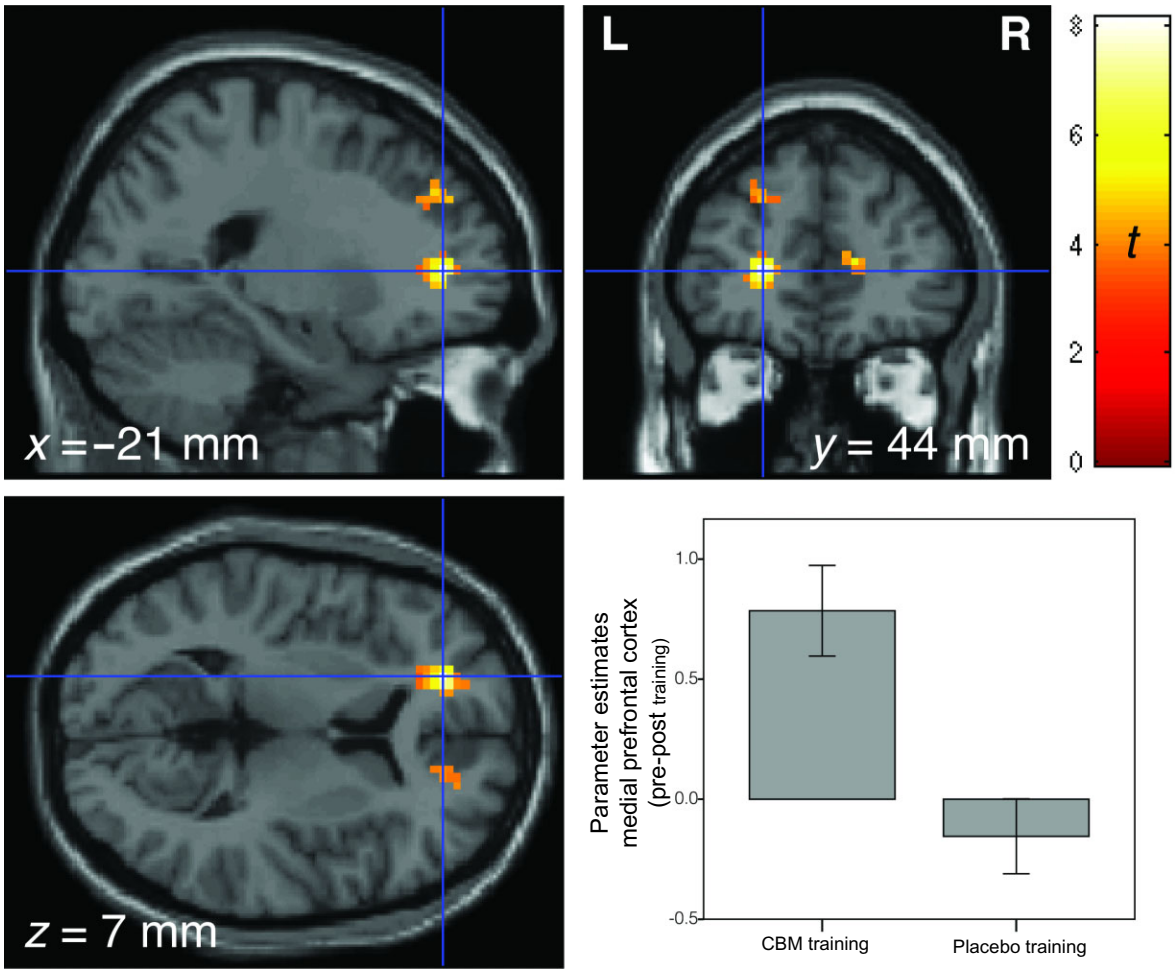

Figure 2 Change of pre-post approach bias-related activations ([alcohol pull > alcohol push] > [soft drink pull > soft drink push]) in the CBM group compared with the placebo group. While mPFC activations reduced after CBM training ($P < 0.05$ FWE SVC), there were no changes after placebo training, not even at $P < 0.005$ uncorrected. Error bars depict 1 SE of the mean. For graphical purposes, significance levels of $P < 0.005$ uncorrected were used to plot activations

with drinking history over all patients ($r = 0.10$, $P = 0.62$). Moreover, the decrease in mPFC activations did not (negatively) correlate with drinking history over all patients ($r = –0.01$ $P = 0.96$), or in one of the groups separately (CBM: $r = –0.39$, $P = 0.19$; placebo: $r = –0.054$, $P = 0.86$). Further, drinking history was not correlated with either DAQ craving ($r = 0.018$, $P = 0.93$) or behavioral approach bias scores before training ($r = 0.012$, $P = 0.95$).

DISCUSSION

Our study is the first in providing evidence that CBM affects neural approach tendencies in the mPFC (dACC and middle frontal gyrus), an area involved in motivation and reward (Hare, Camerer & Rangel 2009; Kahnt *et al.* 2010, 2014; Hare, Malmaud & Rangel 2011; Ludwig *et al.* 2013). We found that before training, the mPFC was activated while approaching versus avoiding alcohol relative to soft drinks, a finding consistent with previous neuroimaging studies on approach/avoidance behavior in alcohol dependence (Ernst *et al.* 2014; Wiers *et al.* 2014b). Three weeks of CBM training led to a reduction in mPFC activation, as compared with the placebo training, in which alcohol cues were pushed and pulled at an equal rate. Moreover, reductions in mPFC activation were correlated with reductions in the behavioral alcohol approach bias scores in the CBM group. That is, both pre-post training reductions of automatic approach bias RTs as well as reductions in self-reported alcohol approach/avoidance inclinations on the AAAQ were associated with reductions in mPFC activation in the CBM group, but not in the placebo group. Because reductions in approach bias scores on the AAT have been shown to mediate reductions in relapse (Eberl *et al.* 2013), and relapse has been associated with elevated alcohol cue-induced mPFC activations (Grusser *et al.* 2004; Beck *et al.* 2012), a decrease in mPFC activation

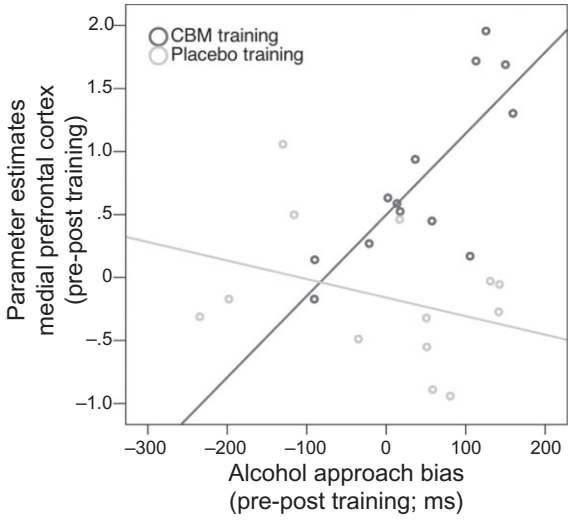

Figure 3 Correlation of pre-post changes in behavioral alcohol approach bias scores (measured outside the scanner) with pre-post changes in approach bias-related mPFC peak activations ([alcohol pull > alcohol push] > [soft drink pull > soft drink push]). In the CBM group (dark gray dots), pre-post changes in behavioral alcohol approach bias scores correlated with pre-post mPFC activations ($r = 0.797$, $P = 0.001$), whereas this was not the case for the placebo training group (light gray dots; $r = -0.128$, $P < 0.05$)

may be important for the previously found relapse-preventing therapeutic effectiveness of CBM (Wiers *et al.* 2011; Eberl *et al.* 2013).

The mPFC (including the ventromedial PFC, [dorsal/rostral] ACC, middle frontal gyrus and orbitofrontal cortex) has been shown to be important for the encoding of the motivational value of rewarding stimuli (Hare *et al.* 2009, 2011; Kahnt *et al.* 2010, 2014; Ludwig *et al.* 2013), and can initiate motor responses to obtain the rewards through its connections with the supplementary motor cortex (Wunderlich, Rangel & O'Doherty 2009). Moreover, increased mPFC activation has been reported in alcohol cue reactivity paradigms in alcohol-dependent patients (Myrick *et al.* 2008; Heinz *et al.* 2009; Koob & Volkow 2010; Goldstein & Volkow 2011; Schacht *et al.* 2013), which was especially elevated in individuals who relapsed three months after scanning versus those who remained abstinent (Grusser *et al.* 2004; Beck *et al.* 2012). The value signal of the mPFC for rewards such as food, cigarettes and cocaine has been shown to be adaptable by means of self-control (Hare *et al.* 2009; Kober *et al.* 2010; Volkow *et al.* 2010; Hollmann *et al.* 2012), attention (Hare *et al.* 2011) and hypnosis (Ludwig *et al.* 2014). In alcohol-dependent patients, Myrick *et al.* (2008) demonstrated that the anticraving medication naltrexone (which was shown to prevent relapse; e.g. Streeton & Whelan 2001) decreased alcohol cue-induced mPFC activation, compared with placebo medication. Even though it remains to be explored whether the mechanisms of CBM are comparable to pharmacological interventions, or to self-control, attention and hypnosis, these studies demonstrate that such interventions are able to modulate alcohol cue-induced mPFC activation.

Our study suggests that CBM reduces the motivational value of alcohol cues encoded in the mPFC by the process of actively avoiding these cues with a joystick. In line with this, the CBM-induced reductions in mPFC activation found in our study were correlated with reductions in both automatic (AAT) and explicit approach inclinations (AAAQ). In previous experiments, the strength of automatic approach tendencies has been positively associated with explicit approach inclinations on the AAAQ in alcohol-dependent patients (Barkby *et al.* 2012). Surprisingly, however, our data did not show an association between reductions in approach inclinations on the AAT and AAAQ, although both measures correlated with mPFC activation. In addition, mPFC reductions were not associated with reductions in subjective alcohol craving. In line with this finding, increased alcohol cue-induced mPFC activation correlated with low striatal dopamine D2 receptor availability but not with craving (Heinz *et al.* 2004). Future studies are necessary to investigate the mechanisms underlying CBM, e.g. by performing training sessions while measuring brain functioning directly.

Some limitations of this study need to be mentioned. Although behavioral effects of CBM on approach bias scores were in the expected direction (an exploratory *t*-test demonstrated that the alcohol approach bias decreased as a trend in the CBM group, whereas not in the placebo group), we could not replicate the behavioral outcome that CBM significantly decreases behavioral approach bias RTs (Wiers *et al.* 2010, 2011; Eberl *et al.* 2013). Because previous studies on CBM consisted of over 200 alcohol-dependent patients (Wiers *et al.* 2011; Eberl *et al.* 2013), and we used different cues for training than for behavioral and neural assessments, it may be that our sample size was too small to find these behavioral effects. Nonetheless, our results show that the effects of CBM training generalize to other non-trained stimuli in terms of neural effects. Further, we neither observed the hypothesized NAcc activations before training nor did we find the hypothesized interaction effect of time × group. Instead, we found that NAcc activations decreased as a main effect of time in subjects pooled over both groups. Moreover, neither alcohol approach bias-related mPFC activations pre-training nor decreases in these mPFC activations after training were related to drinking history of the patients. However, drinking history was also not correlated with either DAQ craving or behavioral approach bias scores before training. It may therefore be that the actual drinking history of patients was related to other factors (e.g. age, body mass index, metabolic rates) rather than craving. As a final point, the current study was

performed in male alcohol-dependent patients only. This was done to minimize confounding factors [e.g. previous studies have shown gender effects in neurobiological reactivity to alcohol stimuli (Seo *et al.* 2011) and effects of CBM on relapse (Wiers *et al.* 2011; Eberl *et al.* 2013)]. Future studies are necessary to test whether CBM has comparable effects in female patients.

In sum, we found that CBM can affect neural approach/avoidance tendencies on the AAT, which was related to decreases in both implicit and explicit measures of approach/avoidance inclinations. A reduction in mPFC (dACC/middle frontal gyrus) responsiveness of the AAT in response to approaching alcohol stimuli may be an underlying mechanism of the therapeutic effectiveness of CBM. Ultimately, neuroimaging measures may prove useful in predicting whether CBM will be effective for individual patients.

Acknowledgements

This study was supported by grants from the German Federal Ministry of Education and Research (BMBF-01KR1207C to A.H. and F.B.) and the German Research Foundation (DFG_FOR_1617 to A.H.). C.E.W. was funded by the Berlin School of Mind and Brain and Humboldt Graduate School. The authors thank Ulrike Malecki, Steffen Pawelczack, Silvia Hoffman, Natalie Becht, Jana Paeplow, Christiane Gawron, Sonja Gröpper, Heiner Stuke, Jenny Parnack and Kristin Trapp for their assistance in recruitment, training and/or testing.

Disclosure/Conflict of Interest

There were no conflicts of interest.

Authors Contribution

All authors were responsible for the study concept and design. CEW and JL recruited alcohol-dependent patients from the clinic. CEW performed measurements and data analyses, and drafted the main part of the manuscript. VUL and TEG assisted in data analyses and in drafting the manuscript. All authors provided critical revision of the manuscript for important intellectual content, critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Whole-brain activations for the alcohol approach bias contrast before training and pre-post training.