



UvA-DARE (Digital Academic Repository)

Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence

Wiers, C.E.; Stelzel, C.; Gladwin, T.E.; Park, S.Q.; Pawelczack, S.; Gawron, C.K.; Stuke, H.; Heinz, A.; Wiers, R.W.; Rinck, M.; Lindenmeyer, J.; Walter, H.; Bermpohl, F.

DOI

[10.1176/appi.ajp.2014.13111495](https://doi.org/10.1176/appi.ajp.2014.13111495)

Publication date

2015

Document Version

Final published version

Published in

The American Journal of Psychiatry

License

Article 25fa Dutch Copyright Act

[Link to publication](#)

Citation for published version (APA):

Wiers, C. E., Stelzel, C., Gladwin, T. E., Park, S. Q., Pawelczack, S., Gawron, C. K., Stuke, H., Heinz, A., Wiers, R. W., Rinck, M., Lindenmeyer, J., Walter, H., & Bermpohl, F. (2015). Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. *The American Journal of Psychiatry*, 172(4), 335-343. <https://doi.org/10.1176/appi.ajp.2014.13111495>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (<https://dare.uva.nl>)

Effects of Cognitive Bias Modification Training on Neural Alcohol Cue Reactivity in Alcohol Dependence

Corinde E. Wiers, Ph.D., Christine Stelzel, Ph.D., Thomas E. Gladwin, Ph.D., Soyoung Q. Park, Ph.D., Steffen Pawelczack, M.Sc., Christiane K. Gawron, Cand.med., Heiner Stuke, M.D., Andreas Heinz, M.D., Ph.D., Reinout W. Wiers, Ph.D., Mike Rinck, Ph.D., Johannes Lindenmeyer, Ph.D., Henrik Walter, M.D., Ph.D., Felix Bermpohl, M.D., Ph.D.

Objective: In alcohol-dependent patients, alcohol cues evoke increased activation in mesolimbic brain areas, such as the nucleus accumbens and the amygdala. Moreover, patients show an alcohol approach bias, a tendency to more quickly approach than avoid alcohol cues. Cognitive bias modification training, which aims to retrain approach biases, has been shown to reduce alcohol craving and relapse rates. The authors investigated effects of this training on cue reactivity in alcohol-dependent patients.

Method: In a double-blind randomized design, 32 abstinent alcohol-dependent patients received either bias modification training or sham training. Both trainings consisted of six sessions of the joystick approach-avoidance task; the bias modification training entailed pushing away 90% of alcohol cues and 10% of soft drink cues, whereas this ratio was 50/50 in the sham training. Alcohol cue reactivity was measured with functional MRI before and after training.

Results: Before training, alcohol cue-evoked activation was observed in the amygdala bilaterally, as well as in the right nucleus accumbens, although here it fell short of significance. Activation in the amygdala correlated with craving and arousal ratings of alcohol stimuli; correlations in the nucleus accumbens again fell short of significance. After training, the bias modification group showed greater reductions in cue-evoked activation in the amygdala bilaterally and in behavioral arousal ratings of alcohol pictures, compared with the sham training group. Decreases in right amygdala activity correlated with decreases in craving in the bias modification but not the sham training group.


Conclusions: These findings provide evidence that cognitive bias modification affects alcohol cue-induced mesolimbic brain activity. Reductions in neural reactivity may be a key underlying mechanism of the therapeutic effectiveness of this training.

Am J Psychiatry 2015; 172:335–343; doi: 10.1176/appi.ajp.2014.13111495

Alcohol dependence is a chronic relapsing disorder, characterized by high levels of craving and the continuation of drinking despite the awareness of negative consequences (1). During the transition from voluntary to impulsive and ultimately habitual drinking, cues associated with alcohol are hypothesized to increase in salience as a result of Pavlovian drug-cue learning (2, 3). As a consequence, alcohol cues engender motivational responses in alcohol-dependent patients, which are triggered relatively automatically (4). Motivational reactivity to alcohol cues has been demonstrated repeatedly in physiological and behavioral studies and is thought to be a key underlying mechanism involved in alcohol craving and alcohol relapse, even after years of abstinence (5).

Incentive-sensitization models of addiction suggest that fronto-limbic dopaminergic neuroadaptations underlie the brain physiology of alcohol cue reactivity. Alcohol intake has

been shown to release dopamine in the ventral tegmental area via interactions with opioid and GABA-ergic neurotransmission, which further projects to mesolimbic structures, such as the nucleus accumbens and the basolateral amygdala, as well as frontal areas (5, 6). Since dopamine signals motivational relevance, it has been hypothesized to be a key neurobiological substrate of drug-cue learning. For example, neuroimaging studies have shown that when alcohol-dependent patients are exposed to alcohol cues, activation in reinforcement-related mesolimbic areas is evoked (5, 7). Reactivity in these areas has been positively related to craving (8–10), to reward processing (11–13), and to alcohol consumption after relapse (7, 14, 15). Although mesolimbic neuroadaptations have been hypothesized to be sustained after years of abstinence (2, 3), studies suggest that only a few weeks of behavioral and/or pharmacological therapy may

 This article is featured in this month's **AJP Audio** and is discussed in an **Editorial** by Dr. O'Brien (p. 305) and **Video** by Dr. Pine

decrease cue-evoked activation in the nucleus accumbens (16, 17) and amygdala (18) in alcohol-dependent individuals. Thus, training effects on nucleus accumbens and amygdala activity may be of particular importance for the ability of interventions to change neural cue reactivity.

Behaviorally, alcohol-dependent patients show an automatic approach bias for alcohol cues, that is, a tendency to more quickly approach than avoid these cues on an approach-avoidance task (9, 19, 20). In this task, participants push and pull pictorial cues with a joystick according to an irrelevant feature such as the format of the cue, and patients have been shown to pull faster than they push alcohol cues (9, 19, 20). The approach bias may reflect an impulsive response toward drug cues and has been positively associated with drug craving (21). Recently, the approach-avoidance task has been adapted into a cognitive bias modification training in which subjects implicitly learn to push away and hence avoid alcohol cues. In heavy drinkers, cognitive bias modification training has been shown to decrease the approach bias and reduce posttraining alcohol intake (22). Moreover, in two recent randomized controlled studies, cognitive bias modification training reduced alcohol craving and relapse rates up to 13% in alcohol-dependent patients, compared with a sham training in which patients pushed and pulled alcohol cues at an equal rate (19) and a non-training group (19, 23). Although these findings show the clinical potential of bias modification in alcohol dependence, it is as yet unclear how bias modification affects brain function. For instance, bias modification could directly reduce the incentive salience of alcohol cues and neural alcohol cue reactivity (2, 24). Understanding the mechanisms underlying cognitive bias modification training can help to further enhance its efficacy and thus further improve the treatment of alcohol dependence.

In this study, using a double-blind randomized design with a sham-training control condition, we examined the effects of cognitive bias modification training on neural reactivity evoked by alcohol cues in alcohol-dependent patients. Patients were randomly assigned to receive either bias modification or sham training, and they performed the approach-avoidance task for 3 weeks. The bias modification group pushed away 90% of alcohol cues, whereas this rate was 50% in the sham training group. Before and after training, neural cue reactivity was measured in functional MRI (fMRI) scans. We expected to find, first, that alcohol cue reactivity would be enhanced in the amygdala and nucleus accumbens across all subjects before training; second, that cue reactivity would decrease in the amygdala and nucleus accumbens as a result of cognitive bias modification; and third, that changes in cue reactivity in these regions would covary with changes in craving.

METHOD

Participants

The Ethical Committee of the Charité–Universitätsmedizin Berlin approved the study, and participants provided written informed consent after receiving a complete description of

the study. Thirty-six male alcohol-dependent inpatients were recruited from the Salus Clinic in Lindow, Germany. Exclusion criteria for all patients were a history of neurological dysfunction, DSM-IV axis I psychiatric disorders other than alcohol dependence (assessed with the Mini International Neuropsychiatric Interview [25]), abstinence from alcohol for >4 months before participation, and intake of psychoactive medication, as tested by urine drug screening. Patients had to be free of psychoactive medication and other drugs for at least 6 months before participation.

Patients were randomly assigned to receive bias modification training or sham training. Two patients did not complete the training (one in each group), and two patients could not be present on the second day of testing for administrative reasons (both in the bias modification group). The final sample consisted of 15 men in the bias modification training group and 17 in the sham training group. Participants completed the Alcohol Dependence Scale to assess severity of dependence (26), the matrix reasoning subtest of the WAIS as a proxy for general intelligence (27), and the State-Trait Anxiety Inventory (28). The groups did not differ significantly in age, years of education, intelligence scores, or clinical variables (Table 1) or in number of smokers (12 in the bias modification group [80%] and 15 in the sham training group [88%]). Smokers were abstinent from tobacco for at least 1.5 hours before scanning.

Experimental Tasks

Approach-avoidance task. The approach-avoidance task was used to measure approach bias before and after training (29). In response to the format of the cue (landscape or portrait), participants pushed and pulled pictures with a joystick, which increased and decreased the size of the cue, respectively; participants had to respond to a cue within 2 seconds. Twenty practice trials were followed by 80 test trials (20 alcohol push, 20 alcohol pull, 20 soft drink push, 20 soft drink pull) that were presented over two blocks. Picture format to response assignment was counterbalanced, and response type assignment did not differ between the two groups. A set of 40 alcohol and 40 soft drink images was used (9).

fMRI cue reactivity. For the fMRI paradigm, the same 80 pictures that were used in the approach-avoidance task were presented over eight blocks per stimulus category. Each block consisted of five stimuli, each presented for 4 seconds. To check whether participants were focused on the task, four oddball blocks were added, containing four alcohol or soft drink stimuli and an oddball cue—a picture of an animal; in these cases, participants had to press a button with their right index finger. The duration of the task was approximately 6 minutes.

Picture rating and craving. After both scanning sessions, pictures were rated for arousal and valence on a 5-point Likert scale, and alcohol craving was assessed with the Desire for Alcohol Questionnaire (30).

Cognitive Bias Modification Training

The cognitive bias modification training scheme, which was an adapted version of the approach-avoidance task, consisted of six training sessions over 3 weeks, each consisting of 400 trials (200 alcohol and 200 soft drink) (19, 23). The experimental bias modification group pushed away 90% and pulled 10% of the alcohol cues (and the reverse for soft drink cues: 10% push and 90% pull). These ratios were 50/50 in the sham training group. Twenty cues were used for training (10 alcohol and 10 soft drink) (19, 23). To test for effects on cue reactivity based on stimulus category (alcohol versus soft drink) rather than on specific pictures, pictures in the training were different but comparable to cues used before and after training in the avoidance task and fMRI cue reactivity.

fMRI acquisition and preprocessing. Scanning was done in a 3-T whole-body MRI scanner (Magnetom Trio Tim, Siemens, Germany) equipped with a 12-channel head coil. A standard T₂-weighted echo planar imaging sequence was used with the following parameters: sequential descending acquisition, repetition time=2 seconds, echo time=25 ms, flip angle=80°, 64×64 pixels in-plane resolution, 34 slices, slice thickness=3 mm, voxel dimensions=3×3×3 mm³, 0.75-mm gap between slides, field of view=192×192 mm², 140 images per session.

Functional data analysis was performed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Scans were spatially realigned, slice-time corrected, and normalized to the standard echo planar imaging template. Smoothing was performed with an 8-mm full width at half maximum Gaussian kernel. Participants did not move more than 2 mm or 2 degrees.

Statistical Analysis

For the approach-avoidance task, responses that were missed or incorrect and response times longer than three standard deviations above the mean were discarded based on each participant's performance. Alcohol approach bias scores were calculated by subtracting median reaction times ([alcohol push – pull] – [soft drink push – pull]). Two-by-two mixed analyses of variance on alcohol approach bias, craving, and picture ratings were calculated, with time (before versus after training) as a within-subject factor and group (bias modification versus sham) as a between-subject factor. Post hoc group comparisons were performed with two-sample t tests at an alpha of 0.05.

Three fMRI regressors—alcohol, soft drink, and oddball blocks (20 seconds each)—were built for every subject and

TABLE 1. Demographic and Clinical Characteristics of Patients Who Received Bias Modification Training or Sham Training

Characteristic	Bias Modification Training		Sham Training		p
	Mean	SD	Mean	SD	
Age (years)	45.33	6.84	42.88	8.31	0.37
Education (years)	10.60	1.45	10.47	1.33	0.79
Wechsler Adult Intelligence Scale score	15.57 ^a	5.20	14.06	5.09	0.42
Duration of abstinence (days)	36.87	27.01	57.35	39.87	0.10
Duration of dependence (years)	17.53	9.74	13.06 ^b	6.88	0.14
Number of detoxifications	5.87 ^c	8.59	3.59 ^d	7.20	0.42
Alcohol intake before admission (grams/day)	332.55	213.65	244.15	164.19	0.20
Alcohol Dependence Scale score	17.87	9.63	14.50	5.45	0.24
Trait Anxiety score	35.21	8.42	34.47	7.42	0.80
State Anxiety score	32.67	8.10	33.82	8.02	0.69

^a N=14.

^b Range, 2–30.

^c Range, 0–26.

^d Range, 0–30.

were convolved with the hemodynamic response function with default temporal filtering of 128 seconds. On the single-subject level, two contrasts were calculated. Contrast 1 was alcohol cue reactivity before training: ([alcohol > soft drink] before training); and contrast 2 was alcohol cue reactivity before and after training: ([alcohol > soft drink] before training) – ([alcohol > soft drink] after training). On the second level, t tests were used to calculate alcohol cue reactivity before training in both groups and between-group alcohol cue reactivity before and after training. Post hoc t tests were used in our a priori regions of interest to explore directions of the interaction of time by group.

Based on our hypotheses, anatomically defined left and right nucleus accumbens and amygdala were chosen as regions of interest (5, 9, 14, 31, 32) and were used for small-volume correction of the results, with a significance threshold of 0.05, family-wise error corrected. Exploratory whole-brain analyses are presented in the data supplement that accompanies the online edition of this article.

Behavioral approach bias scores, craving, and alcohol picture ratings before training were correlated with blood-oxygen-level-dependent (BOLD) contrast 1 (alcohol cue reactivity before training) using our regions of interest. For behavioral variables showing a positive correlation in our regions of interest before training, we computed difference scores for before and after training and correlated these with significant activations in BOLD contrast 2 (alcohol cue reactivity before and after training).

RESULTS

Behavioral Effects of Cognitive Bias Modification Training

Approach-avoidance task. Alcohol approach bias scores before and after training, as well as difference scores, were distributed normally in both groups (Kolmogorov-Smirnov test, all p values >0.62). Mean error rates were 3.04% (SD=3.22) before training and 2.65% (SD=3.83)

after training, collapsed across the groups. There were no main effects of group or time and no interaction effect of group by time.

For the alcohol approach bias scores, there was no significant interaction effect of group by time, and there were no main effects. Exploratory *t* tests showed that the groups did not differ before and after training and that a decrease in mean reaction time approached significance in the cognitive bias modification training group (before training, mean=11.90, SD=64.01; after training, mean=-25.53, SD=55.80; $t=1.18$, $df=14$, $p=0.091$) but not in the sham training group (before training, mean=-9.35, SD=122.21; after training, mean=21.50, SD=99.89; $t=-0.64$, $df=16$, $p=0.53$).

Subjective alcohol craving and picture ratings. For craving scores, there was a main effect of time ($F=9.32$, $df=1, 30$, $p=0.005$; $\eta^2=0.23$). In both groups, craving scores were higher before training (bias modification group, mean=15.20, SD=6.95; sham training, mean=12.29, SD=5.01) than after (bias modification group, mean=12.33, SD=6.20; sham training, mean=10.36, SD=3.62). There was no significant interaction effect of group by time for craving scores. Exploratory paired *t* tests showed that the groups did not differ before and after training, but craving scores significantly decreased in the bias modification group ($t=3.86$, $df=14$, $p=0.002$) but not in the sham training group.

There was a significant interaction effect of group by time for arousal ratings of alcohol pictures ($F=4.19$, $df=1, 30$, $p=0.05$; $\eta^2=0.12$), with arousal ratings having a nearly significant decrease in the bias modification training group (before training, mean=1.02, SD=0.40; after training, mean=0.88, SD=0.51; $t=2.01$, $df=14$, $p=0.064$) but not in the sham training group (before training, mean=0.98, SD=0.34; after training, mean=1.04, SD=0.38; $t=0.82$, $df=16$, $p=0.43$). There were no significant effects of group by time for valence ratings. Before and after training, the groups did not differ in arousal and valence.

Cue-Evoked Brain Activation Within and Between Groups

All patients paid attention to the cue reactivity task, as shown by their responses to all four oddball cues, before and after training.

Before training, subjects pooled across both groups showed alcohol cue-evoked activity in the amygdala bilaterally (peak Montreal Neurological Institute coordinates, left side: -21, -7, -14; $t=4.98$, $df=31$, $p<0.001$; right side: 21, -7, -17; $t=2.87$, $df=31$, $p=0.052$) while viewing alcohol cues compared with viewing soft drink cues. In this contrast, the right nucleus accumbens was also activated, although the effect fell short of significance (peak coordinates: 8, 8, -11; $t=2.48$, $df=31$, $p=0.057$). Figure 1 illustrates the pretraining activations in the amygdala and nucleus accumbens. (See Table S1 in the online data supplement for whole brain activations showing no relevant between-group differences before training.)

In the assessment of group differences in alcohol cue reactivity before and after training, the bias modification

group showed significantly greater reductions in alcohol cue-evoked activation in the amygdala bilaterally (peak coordinates, left side: -15, -1, -23; $t=2.97$, $df=30$, $p<0.05$; right side: 27, 2, -20; $t=3.08$, $df=30$, $p<0.05$) compared with the sham training group (Figure 2). This effect was not present for the nucleus accumbens, even at a more liberal threshold of $p<0.005$ uncorrected. After training, the bias modification group had significantly lower activation in the left amygdala than the sham training group (peak coordinates: -15, -1, -26; $t=3.86$, $df=30$, $p<0.05$). (See Table S1 in the online data supplement for whole brain activations.)

Post hoc *t* tests on cue reactivity before and after training within groups demonstrated a significant reduction of left and right amygdala activity in the bias modification group (peak coordinates, left side: -27, 2, -17; $t=3.58$, $df=14$, $p<0.05$; right side: 24, 2, -20; $t=2.88$, $df=14$, $p<0.05$). However, this was not the case for the sham training group, even at $p<0.005$ uncorrected.

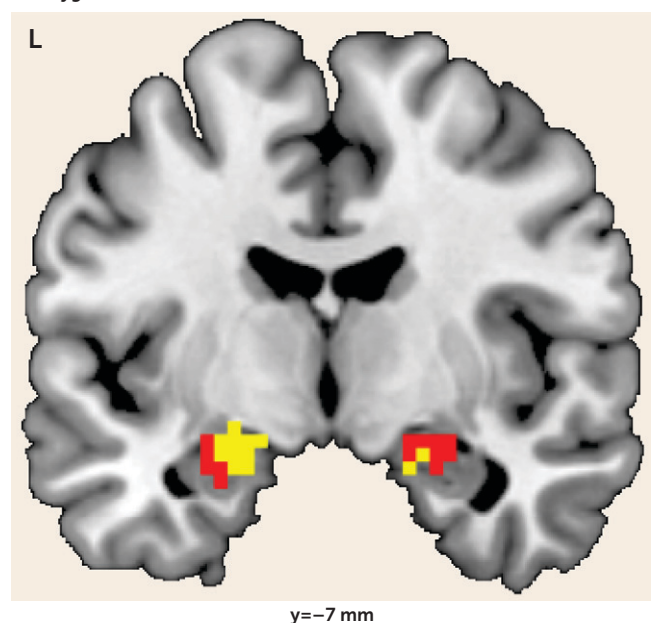
Correlations With Behavioral Measures

Before training, both groups' craving scores significantly correlated with alcohol cue-induced amygdala activity bilaterally (coordinates, left side: -18, -7, -17; $t=6.15$, $df=31$, $p<0.001$; right side: 21, -4, -23; $t=3.88$, $df=31$, $p<0.01$). Craving scores were correlated with activity in the right nucleus accumbens, but the effect fell short of significance (peak coordinates: 15, 11, -8; $t=2.15$, $df=31$, $p=0.057$). Arousal ratings also correlated with cue reactivity in the left and right amygdala (coordinates, left side: -27, -4, -20; $t=3.67$, $df=31$, $p=0.01$; right side: 21, -1, -14; $t=3.46$, $df=31$, $p<0.05$), and in the right nucleus accumbens, although again falling just short of significance (peak coordinates: 18, 8, -11; $t=2.51$, $df=31$, $p=0.052$). Alcohol approach bias scores and valence ratings did not correlate with alcohol cue-induced activations in our regions of interest.

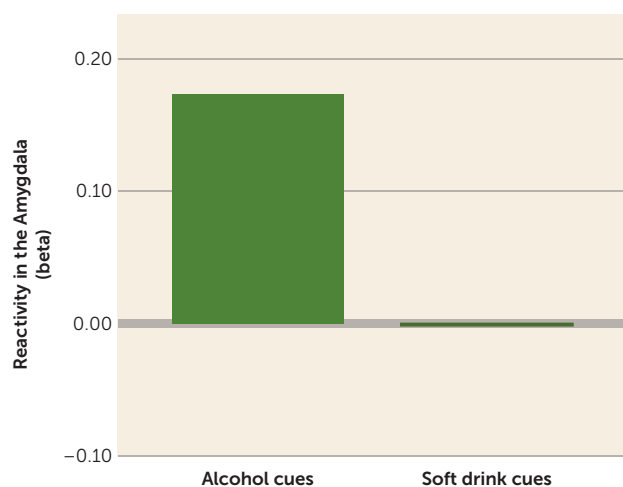
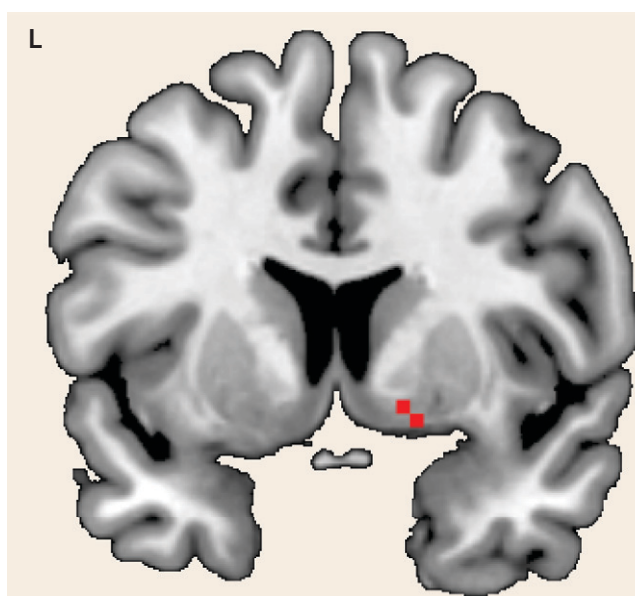
In the bias modification group, the difference in right amygdala activity before and after training correlated positively with the decrease in alcohol craving (peak coordinates: 30, 2, -17; $t=3.44$, $df=14$, $p<0.05$), but not in the sham training group. Moreover, when the correlation slopes of cue reactivity and craving before and after treatment were compared between the two groups, there was an effect in the right amygdala (peak coordinates: 30, 2, -17; $t=3.85$, $df=30$, $p<0.01$), providing stronger evidence for a greater correlation in bias modification (Figure 3). There were no significant correlations between decreases in arousal ratings and decreases in amygdala activation. See Table S2 in the online data supplement for exploratory analyses of alcohol cue reactivity and relapse rates 1 year after training.

DISCUSSION

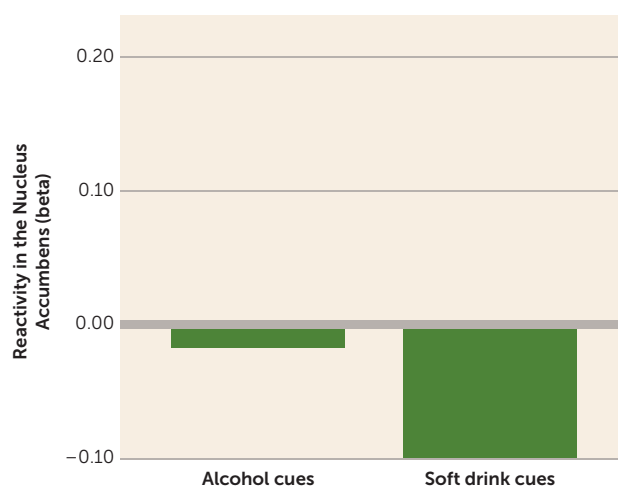
Our aim in this study was to examine the effects of cognitive bias modification training on neural alcohol cue reactivity. The results provide first evidence that cognitive bias modification training can affect cue-induced amygdala activity, an

FIGURE 1. Baseline Alcohol Cue Reactivity in the Amygdala and Nucleus Accumbens in Alcohol-Dependent Patients^a**A. Amygdala**

y = -7 mm

**B. Nucleus Accumbens**

y = 8 mm



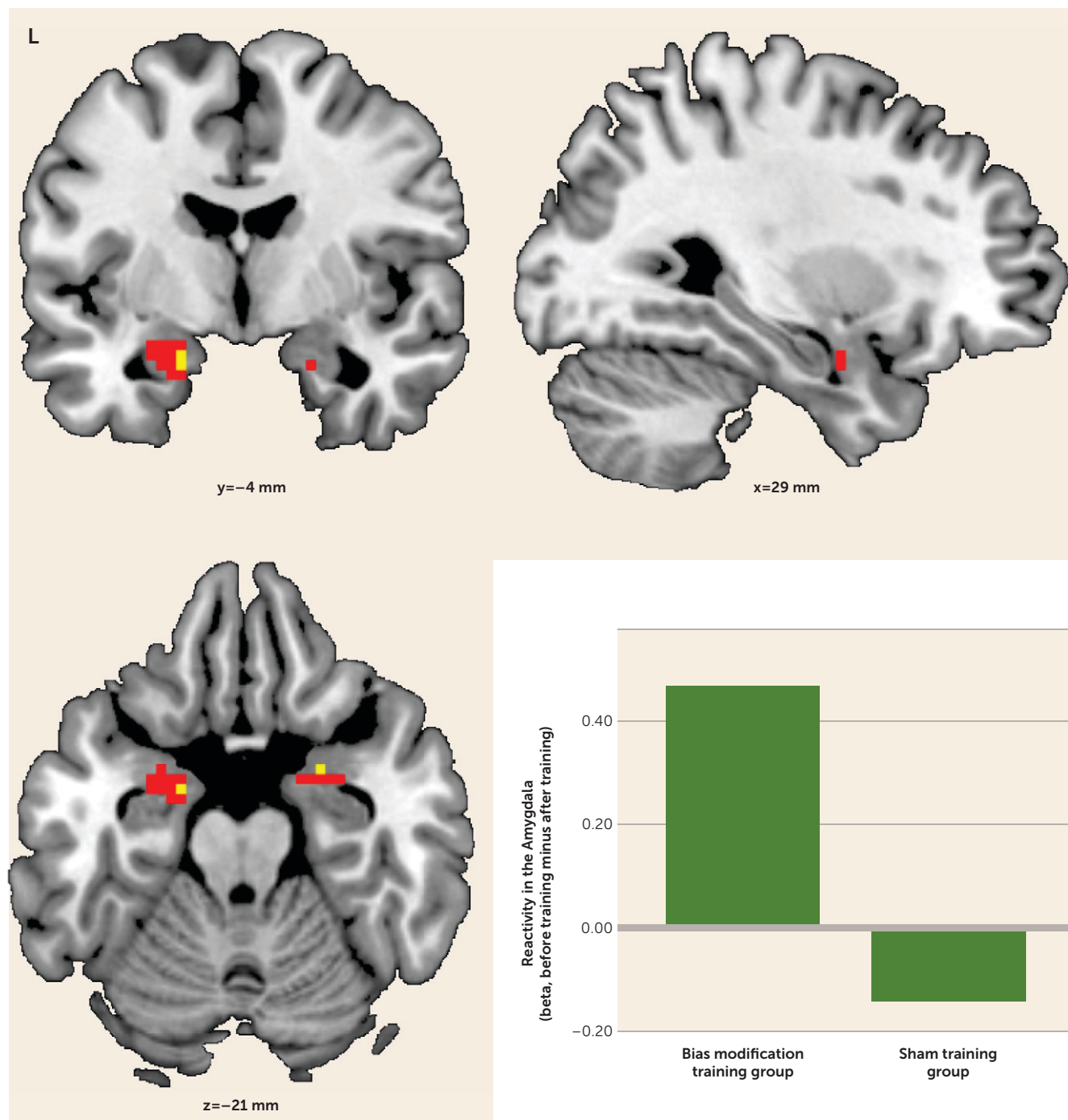
^a Before training, both groups of alcohol-dependent patients showed significant alcohol cue reactivity (alcohol – soft drink) in the left and right amygdala (panel A; $p < 0.05$, family-wise error corrected, small-volume corrected), as well as reactivity approaching significance in the right nucleus accumbens (panel B; $p = 0.057$, family-wise error corrected, small-volume corrected). For graphical purposes, significance levels of 0.05 (red) and 0.005 (yellow) uncorrected were used to plot activations. Activations in both areas correlated with alcohol craving scores and arousal ratings of alcohol cues.

area previously associated with alcohol cue reactivity, alcohol craving, and relapse prediction (5, 7–9, 12, 14, 15, 17). Before training, both groups showed alcohol cue reactivity in the amygdala and in the nucleus accumbens (although the latter fell short of significance), which correlated positively with craving scores and arousal ratings of alcohol cues. These findings replicate previous studies of alcohol dependence and suggest that alcohol cue reactivity may be related to clinical severity of dependence (5, 7–9, 12, 33). When comparing alcohol cue-evoked brain reactivity before and after training, amygdala activity differed between the two groups: while amygdala activity decreased in the bias modification group, this effect was not observed in the sham

training group. Moreover, the decrease in right amygdala activity correlated with a decrease in alcohol craving scores in the bias modification group, but not in the sham training group. Therefore, reduction of alcohol cue-induced amygdala activity may be an important underlying mechanism contributing to the previously reported therapeutic effectiveness of cognitive bias modification training (19, 23) and may serve as a biomarker for reductions in clinically relevant alcohol craving.

The amygdala has been shown to play a central role in Pavlovian conditioned learning, the modulation of incentive salience to reward cues, and the formation and consolidation of emotional memories (12, 34). In recent work, a function of

FIGURE 2. Change in Cue Reactivity in Alcohol-Dependent Patients Who Received Bias Modification Training or Sham Training^a

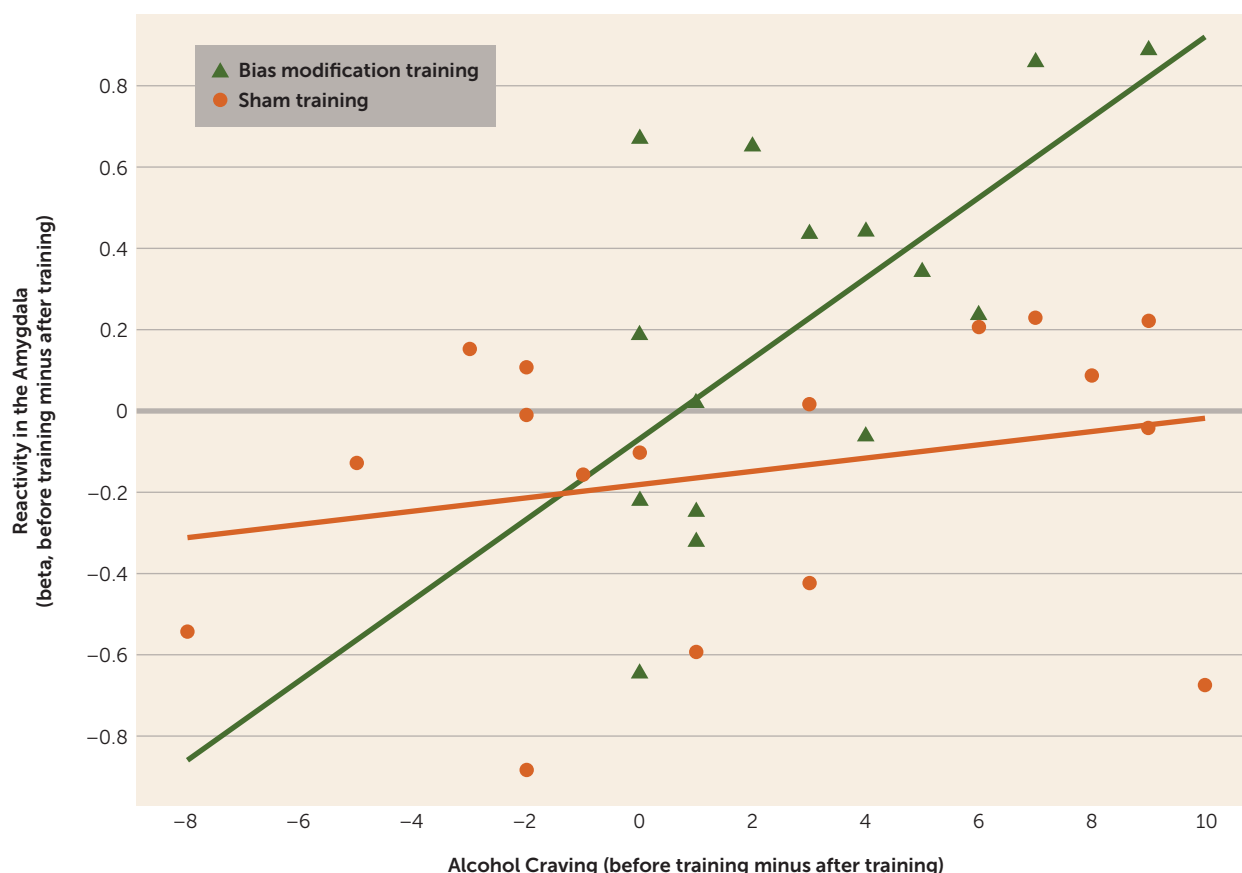


^a While amygdala activation decreased bilaterally over the course of training in the bias modification training group ($p < 0.05$, family-wise error corrected, small-volume corrected), there was no reduction in the sham training group, even at $p < 0.005$ uncorrected. For graphical purposes, significance levels of 0.05 (red) and 0.005 (yellow) uncorrected were used to plot activations.

the amygdala has been described as the processing of the personal motivational salience of stimuli (35). The region has been associated with craving while passively viewing drug cues in drug-dependent patients (12, 36) and in approaching versus avoiding alcohol cues on the approach-avoidance task (9), and two recent studies found that increased alcohol cue reactivity in the amygdala was predictive of alcohol

relapse after abstinence (14, 15). A study by Schneider et al. (18) showed that the combination of pharmacological and behavioral therapy reduced amygdala activity when smelling alcohol in alcohol-dependent patients, whereas a healthy comparison group did not show reductions in amygdala activation over the same period. Although the Schneider et al. study could not distinguish whether the effect was due

FIGURE 3. Correlation of Alcohol Craving and Change in Cue Reactivity of the Right Amygdala After Bias Modification Training or Sham Training in Alcohol-Dependent Patients^a



^a The graph shows the correlation of the amygdala cue reactivity change before and after training with scores on the Desire for Alcohol Questionnaire in the two groups. In the bias modification training group, the difference between right amygdala activations before and after treatment correlated significantly with the decrease in alcohol craving ($p < 0.05$, family-wise error corrected, small-volume corrected), whereas this was not the case for the sham training group, even at $p < 0.005$ uncorrected. Beta values of activations were extracted per subject at $p = 0.005$ uncorrected.

to behavioral or pharmacological interventions, it showed that the amygdala can be flexibly modulated over time with respect to alcohol-induced cue reactivity. Moreover, it has recently been shown (37) that emotional cue-evoked amygdala activity can be modulated by attentional bias modification in anxious individuals. A possible interpretation of our results, in which bias modification was found to reduce amygdala cue reactivity, is that bias modification reduces the motivational salience of alcohol cues. In line with this interpretation, we found that bias modification reduced arousal ratings of alcohol cues. Moreover, bias modification-induced reductions in right amygdala activation correlated with reductions in alcohol craving.

How might cognitive bias modification cause such a reduction in salience? It may be that this effect is related to findings on inhibition training (38–40). These studies have shown that the inhibition of responses to initially positively valenced stimuli results in a devaluation of that stimulus category. Hypothetically, the requirement to consistently perform incongruent actions in approach/avoidance modification (i.e., actively and habitually avoid previously desired

alcohol cues) causes a similar effect: patients could solve the avoid-alcohol problem by reducing the overall salience of alcohol cues (24) and hence reduce behavioral biases associated with them. It therefore may be that reducing overall salience is easier to achieve than changing the automatic response bias without reducing salience. Additional research is needed to provide evidence for or against the hypothesis that the mediating mechanism of cognitive bias modification involves, at least partially, reductions in the salience of alcohol cues.

Despite significant effects of cognitive bias modification on neural cue reactivity, its correlation with craving, and behavioral effects on arousal ratings, we could not replicate the interaction effect of group by time on approach bias scores found by Eberl et al. (23) and Wiers et al. (19, 22). Since effects of bias modification on approach bias and alcohol craving are in the hypothesized direction—we observed a reduction in approach bias (falling short of significance) as well as a significant reduction in craving in the bias modification training group but not in the sham training group—it is likely that the lack of effect is due to the relatively small sample size in this study. Although behavioral effects of

training have been observed in sample sizes of 200 to 500 (19, 23), sample sizes of around 15 alcohol-dependent patients have been shown to be sufficient to measure alcohol cue-evoked neural activity (7, 16) and reductions in cue reactivity over time (16–18). Moreover, to allow training effects to generalize to general alcohol stimuli, patients were trained on different cues than those used for behavioral and neural assessments. This was not the case in previous studies, and this conservative approach may have led to less power for the behavioral effect. Nevertheless, our results show that the effects of bias modification generalize to other, nontrained stimuli, at least in terms of neural effects and in arousal ratings of alcohol cues. Furthermore, we scanned patients after 1 month of abstinence on average, which may have reduced the likelihood of detecting effects of training on behavior and brain activation. This may explain the weak initial activation of the nucleus accumbens before training and the fact that we did not observe the hypothesized difference in reductions in the nucleus accumbens between groups. Another limitation is that our study assessed craving as a clinical outcome measure but was not designed to detect between-group differences in relapse. We assessed relapse 1 year after our assessment of abstinence (reported in the online data supplement), but our study was underpowered to detect cue reactivity effects for relapse. Nevertheless, behavioral craving (10) and amygdala cue reactivity have been shown to predict relapse in alcohol dependence (14, 15), providing further evidence that alcohol cue-induced amygdala reactivity is important for clinical success in alcohol dependence. Studies with larger sample sizes are needed to explore whether the neural effects of cognitive bias modification training in the amygdala are not only associated with alcohol craving, but also can predict relapse status.

In conclusion, we show here for the first time that cognitive bias modification training affects alcohol cue reactivity, which was associated with reductions in alcohol craving. These results suggest that bias modification can reduce the motivational salience of drug cues encoded in the amygdala. Such findings can help us better understand the underlying mechanisms of the clinical effects of cognitive bias modification, which can lead to improved training schemes. Furthermore, fMRI measurements may prove useful in predicting whether cognitive bias modification will be effective for individual patients.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry and Psychotherapy and the Berlin Center for Advanced Neuroimaging, Charité–Universitätsmedizin Berlin; the Berlin School of Mind and Brain and the Department of Psychology, Humboldt Universität zu Berlin; the Department of Education and Psychology, Freie Universität Berlin; the Addiction, Development, and Psychopathology Lab, Department of Psychology, University of Amsterdam, Amsterdam; the Department of Psychology, University of Lübeck, Lübeck, Germany; the Salus Klinik, Lindow, Germany; the Behavioral Science Institute, Radboud University, Nijmegen, the Netherlands; and Chemnitz University of Technology, Chemnitz, Germany.

Address correspondence to Dr. C.E. Wiers (corinde.wiers@nih.gov).

Dr. Walter and Dr. BERPPOHL contributed equally.

Supported by grants from the German Federal Ministry of Education and Research (BMBF-01KR1207C to Dr. Heinz and Dr. BERPPOHL) and the German Research Foundation (DFG_FOR_1617 to Dr. Heinz).

The authors thank Ulrike Malecki, Silvia Hoffman, Natalie Becht, Jana Paeplow, and Sébastien Lehmann for their assistance in recruitment, screening, and training; Kristin Trapp, Sonja Gröpper, and Jenny Parnack for assistance in data acquisition; Catherine Hindi Attar and Stephanie Spengler for help with data analysis; and the subjects who volunteered to participate in the study.

Dr. Gladwin has received research funding from the European Foundation for Alcohol Research. Dr. R.W. Wiers has received research funding from the Netherlands Science Foundation (NWO), the Medical Research Council Netherlands, the European Commission Seventh Framework Program (FP7), the European Foundation for Alcohol Research, Amsterdam University Funds, the Dutch Ministry of Justice and Security, and NIDA-NWO, and he has received a speaking fee from Lundbeck. Dr. Walter has received funding from the German Ministry of Education, the German Research Foundation, and the Volkswagen Foundation; he has served as a reviewer for the Netherlands Organization for Scientific Research, as a speaker for Humboldt University, West German Broadcasting, Law Academy of North-Rhine-Westphalia, University of Mainz, and the XV Congress of Cognitive Psychotherapy in Milan, and as editor for the journal *Nervenheilkunde*. Dr. BERPPOHL has received grant support from the German Research Foundation (grant DFG BE 2611/2-1) and the German Federal Ministry of Education and Research (grant 01KR1207C) and travel grants from Eli Lilly International Foundation and Lundbeck. The other authors report no financial relationships with commercial interests.

Received Nov. 13, 2013; revisions received Jan. 17, June 17, and Sept. 3, 2014; accepted Sept. 12, 2014.

REFERENCES

1. Stacy AW, Wiers RW: Implicit cognition and addiction: a tool for explaining paradoxical behavior. *Annu Rev Clin Psychol* 2010; 6: 551–575
2. Robinson TE, Berridge KC: The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 1993; 18:247–291
3. Robinson TE, Berridge KC: Addiction. *Annu Rev Psychol* 2003; 54: 25–53
4. Wiers RW, Bartholow BD, van den Wildenberg E, et al: Automatic and controlled processes and the development of addictive behaviors in adolescents: a review and a model. *Pharmacol Biochem Behav* 2007; 86:263–283
5. Heinz A, Beck A, Grüsser SM, et al: Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addict Biol* 2009; 14: 108–118
6. Hyman SE, Malenka RC: Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci* 2001; 2:695–703
7. Grüsser SM, Wrase J, Klein S, et al: Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology (Berl)* 2004; 175:296–302
8. Myrick H, Anton RF, Li X, et al: Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. *Neuropsychopharmacology* 2004; 29:393–402
9. Wiers CE, Stelzel C, Park SQ, et al: Neural correlates of alcohol-approach bias in alcohol addiction: the spirit is willing but the flesh is weak for spirits. *Neuropsychopharmacology* 2014; 39:688–697
10. Heinz A, Siessmeier T, Wrase J, et al: Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: a combined [18F]DOPA and [18F]DMFP PET study in detoxified alcoholic patients. *Am J Psychiatry* 2005; 162:1515–1520

11. Park SQ, Kahnt T, Rieskamp J, et al: Neurobiology of value integration: when value impacts valuation. *J Neuroscience* 2011; 31:9307–9314
12. Koob GF, Volkow ND: Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; 35:217–238
13. Wrase J, Grusser SM, Klein S, et al: Development of alcohol-associated cues and cue-induced brain activation in alcoholics. *Eur Psychiatry* 2002; 17:287–291
14. Beck A, Wüstenberg T, Genauck A, et al: Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. *Arch Gen Psychiatry* 2012; 69:842–852
15. Jorde A, Bach P, Witt SH, et al: Genetic variation in the atrial natriuretic peptide transcription factor GATA4 modulates amygdala responsiveness in alcohol dependence. *Biol Psychiatry* 2014; 75:790–797
16. Vollstädt-Klein S, Loeber S, Kirsch M, et al: Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. *Biol Psychiatry* 2011; 69:1060–1066
17. Myrick H, Li X, Randall PK, et al: The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. *J Clin Psychopharmacol* 2010; 30:365–372
18. Schneider F, Habel U, Wagner M, et al: Subcortical correlates of craving in recently abstinent alcoholic patients. *Am J Psychiatry* 2001; 158:1075–1083
19. Wiers RW, Eberl C, Rinck M, et al: Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome. *Psychol Sci* 2011; 22:490–497
20. Ernst LH, Plichta MM, Dresler T, et al: Prefrontal correlates of approach preferences for alcohol stimuli in alcohol dependence. *Addict Biol* 2014; 19:497–508
21. Wiers CE, Kühn S, Javadi AH, et al: Automatic approach bias towards smoking cues is present in smokers but not in ex-smokers. *Psychopharmacology (Berl)* 2013; 229:187–197
22. Wiers RW, Rinck M, Kordts R, et al: Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. *Addiction* 2010; 105:279–287
23. Eberl C, Wiers RW, Pawelczack S, et al: Approach bias modification in alcohol dependence: do clinical effects replicate and for whom does it work best? *Dev Cogn Neurosci* 2013; 4:38–51
24. Wiers RW, Gladwin TE, Rinck M: Should we train alcohol-dependent patients to avoid alcohol? *Front Psychiatry* 2013; 4:33
25. Sheehan DV, Lecrubier Y, Sheehan KH, et al: The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59(suppl 20):22–33
26. Skinner HA, Allen BA: Alcohol dependence syndrome: measurement and validation. *J Abnorm Psychol* 1982; 91:199–209
27. Kaufman AS, Lichtenberger E: *Assessing Adolescent and Adult Intelligence*, 3rd ed. Hoboken, NJ, Wiley, 2006
28. Spielberger CD, Gorsuch RL, Lushene R, et al: *Manual for the State-Trait Anxiety Inventory*. Palo Alto, Calif, Consulting Psychologists Press, 1983
29. Wiers RW, Rinck M, Dictus M, et al: Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1 G-allele. *Genes Brain Behav* 2009; 8:101–106
30. Love A, James D, Willner P: A comparison of two alcohol craving questionnaires. *Addiction* 1998; 93:1091–1102
31. Robbins TW, Everitt BJ: Drug addiction: bad habits add up. *Nature* 1999; 398:567–570
32. Maldjian JA, Laurienti PJ, Kraft RA, et al: An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; 19:1233–1239
33. Schacht JP, Anton RF, Myrick H: Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addict Biol* 2013; 18:121–133
34. Mahler SV, Berridge KC: Which cue to “want”? Central amygdala opioid activation enhances and focuses incentive salience on a prepotent reward cue. *J Neurosci* 2009; 29:6500–6513
35. Cunningham WA, Brosch T: Motivational salience: amygdala tuning from traits, needs, values, and goals. *Curr Dir Psychol Sci* 2012; 21: 54–59
36. Childress AR, Mozley PD, McElgin W, et al: Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 1999; 156:11–18
37. Taylor CT, Aupperle RL, Flagan T, et al: Neural correlates of a computerized attention modification program in anxious subjects. *Soc Cogn Affect Neurosci* 2014; 9:1379–1387
38. Veling H, Aarts H: Putting behavior on hold decreases reward value of need-instrumental objects outside of awareness. *J Exp Soc Psychol* 2009; 45:1020–1023
39. Veling H, Holland RW, van Knippenberg A: When approach motivation and behavioral inhibition collide: behavior regulation through stimulus devaluation. *J Exp Soc Psychol* 2008; 44:1013–1019
40. Houben K, Nederkoorn C, Wiers RW, et al: Resisting temptation: decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug Alcohol Depend* 2011; 116:132–136