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The automatic pull of drug cues in addiction: Neural correlates and effects of re-training

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i. Abstract

Addiction is a chronic, relapsing brain disorder, characterized by continuation of drug-use despite knowledge of the negative consequences. One important factor for relapse may be the degree to which drug cues automatically trigger motivational approach responses (i.e., "drug cue reactivity"). This phenomenon is hypothesized to be the result of neuroadaptations in mesocorticolimbic areas. Empirical studies indeed demonstrate that drug-addicted individuals have a tendency to faster approach than avoid drug cues compared to neutral cues (i.e., a drug approach bias), which has been associated with higher drug craving and relapse. Moreover, retraining the drug approach bias with Cognitive Bias Modification training (CBM) in alcohol-dependent patients has been shown to reduce relapse rates one year after training. These findings highlight the clinical importance of the drug approach bias. However, much remains unknown about the persistence of the approach bias after drug abstinence, the neural correlates underlying the approach bias, and neural mechanisms of CBM.

The overall aim of this thesis is to study automatic approach/avoidance behaviour in tobacco and alcohol dependence. More specifically, the thesis aims to answer the following four questions: first, do drug-dependent individuals have an automatic approach bias for drug cues and is the strength of this bias related to craving? Second, does the drug approach bias persist after prolonged abstinence? Third, what are the underlying neural correlates of the drug approach bias? Fourth, what are the effects of CBM on neural drug cue reactivity in drug-dependence?

For this purpose, three empirical studies were conducted. First, we investigated the approach bias to smoking cues and alcohol cues on the Approach Avoidance Task (AAT) in heavy tobacco smokers and alcohol-dependent patients respectively, and studied its relation to subjective drug craving (experiment I and II). Second, we compared heavy smokers, never-smokers and abstinent heavy smokers (i.e., ex-smokers) on the automatic approach bias to smoking cues (experiment I). Third, we examined alcohol-dependent patients and healthy controls with functional magnetic resonance imaging (fMRI), while they performed the AAT and correlated approach bias-related activation with alcohol craving (experiment II). Fourth, in a double-blind placebo-controlled randomized design, alcohol-dependent patients were assigned to a CBM group or a placebo training group and were trained with CBM/placebo training for three weeks. Before and after training, alcohol cue-evoked brain reactivity was measured with fMRI (experiment III).

The following key results were obtained: first, heavy smokers and alcohol-dependent patients showed an automatic drug approach bias compared to non-addicted control groups. In

smokers but not in alcohol-dependent patients, drug approach tendencies correlated with drug craving scores. Second, ex-smokers had diminished smoking approach tendencies compared to heavy smokers. No group differences on these scores were found between ex-smokers and never-smokers. Third, alcohol-dependent patients showed larger blood-oxygen-level dependent responses in the nucleus accumbens and medial prefrontal cortex compared to healthy controls; these regions are involved in reward and motivational processing. In patients, alcohol craving scores were positively correlated with alcohol approach bias-related amygdala activation. Finally, alcohol-dependent patients who performed CBM showed greater reductions in cue-evoked activation in the bilateral amygdala, compared to patients who performed placebo training. Decreases in craving scores were correlated with decreases in amygdala activity within the CBM group but not in the placebo group.

These findings suggest that the automatic drug approach bias is present in various drug-addicted populations, and is not strictly permanent, as has been suggested by incentive sensitisation models of addiction, but rather can diminish after long-term drug cessation. In line with such models, however, mesolimbic brain regions that play a key role in reward and motivation are associated with the automatic alcohol approach bias in alcohol-dependent patients. CBM can affect cue-induced mesolimbic brain activity in alcohol-dependent patients, which may be an underlying mechanism of the therapeutic effectiveness of CBM and of successful abstinence in general. In summation, this dissertation suggests the automatic drug approach bias as a promising target for clinical intervention.

ii. Zusammenfassung

Sucht ist eine chronische Gehirnerkrankung, charakterisiert durch hohe Rückfallraten und die Fortsetzung des Substanzkonsums trotz negativer Konsequenzen. Was zu Rückfällen wesentlich beiträgt, ist möglicherweise eine automatische, motivationale Annäherungsreaktion (i.e. „Cue-Reaktivität“), die von Substanzreizen ausgelöst wird. Diese Reaktion geschieht meistens unbewusst und ist vermutlich das Ergebnis neuronaler Veränderungen in mesocorticolimbischen Hirnarealen. Empirische Studien zeigen, dass Menschen mit Substanzabhängigkeit eine automatische Tendenz haben, sich substanzbezogenen Bildern anzunähern, anstatt sie zu vermeiden (d.h., einen Substanz-Annäherungsbias). Diese Tendenz ist mit höherem Suchtverlangen und höheren Rückfallraten assoziiert. Des Weiteren wurde vor kurzem herausgefunden, dass ein „Modifikationstraining des kognitiven Bias“ (CBM) bei alkoholabhängigen Patienten gute klinische Effekte hinsichtlich der Rückfallraten ein Jahr nach dem Training zeigt. Diese Befunde unterstreichen die klinische Relevanz des Annäherungsbias bei Menschen mit Substanzabhängigkeit. Allerdings ist wenig über das Fortbestehen des Annäherungsbias bei Abstinenz, die zugrunde liegenden neuronalen Korrelate des Annäherungsbias und die neuronalen Mechanismen des CBMs bekannt.

Ziel dieser Dissertation ist es, automatische Annäherungstendenzen bei Menschen mit Tabak- und Alkoholabhängigkeit zu untersuchen. Im Detail hat die Dissertation das Ziel, die folgenden vier Fragen zu beantworten: 1. Zeigen Menschen mit Substanzabhängigkeit einen Annäherungsbias für substanzbezogene Bilder und ist die Stärke des Annäherungsbiases mit dem subjektiven Verlangen nach dem Substanz assoziiert? 2. Ist der Annäherungsbias auch nach längerer Substanzabstinenz stabil? 3. Was sind die neuronalen Korrelate des visuellen Substanz-Annäherungsbias? 4. Was sind die neuronalen Effekte von CBM auf die Cue-Reaktivität bei Menschen mit Substanzabhängigkeit?

Dazu wurden drei empirische Studien durchgeführt. 1. Es wurde untersucht, ob starke Raucher und alkoholabhängige Patienten einen Annäherungsbias beim Approach Avoidance Task (AAT) zeigen und ob dieser Bias mit dem subjektiven Suchtverlangen korreliert (Experiment I und II). 2. Es wurden drei Gruppen – starke Raucher, Nichtraucher und ehemalige starke Raucher (d.h., Ex-Raucher) – im Hinblick auf Annäherungstendenzen für Rauchstimuli untersucht (Experiment I). 3. Es wurden alkoholabhängige Patienten und gesunde Kontrollprobanden mit Hilfe der funktionellen Magnetresonanztomographie (fMRT) während der Durchführung der AAT untersucht und getestet, ob der im fMRT beobachtete

Annäherungsbias mit dem subjektiven Verlangen nach Alkohol korreliert (Experiment II). 4. Es wurden in einem doppelblinden, Placebo-kontrollierten, randomisierten Design alkoholabhängige Patienten in eine CBM-Gruppe oder eine Placebo-Trainingsgruppe eingeteilt, bevor sie drei Wochen ein CBM- bzw. Placebo-Training ausführten. Vor und nach dem Training wurde die Alkohol-Cue-Reaktivität mit Hilfe des fMRT gemessen (Experiment III).

Es ergaben sich folgende Hauptergebnisse: 1. Starke Raucher und alkoholabhängige Patienten zeigten im Vergleich zu nicht-abhängigen Kontrollgruppen einen automatischen Substanz-Annäherungsbias. Bei Rauchern, jedoch nicht bei alkoholabhängigen Patienten, korrelierte diese Annäherungstendenz mit dem Suchtverlangen. 2. Ehemalige Raucher zeigten im Vergleich zu starken Rauchern eine verminderte Annäherungstendenz für Rauchstimuli. Hierbei fand sich kein Unterschied zwischen der Gruppe der ehemaligen Raucher und der Nichtraucher. 3. Alkoholabhängige Patienten zeigten im Vergleich zu der gesunden Kontrollgruppe ein höheres Blood-Oxygen-Level Dependent (BOLD)-Signal im Nucleus Accumbens und im medialen präfrontalen Kortex. Dies sind Regionen, die eine zentrale Rolle bei motivationalen Prozessen spielen. Bei den Patienten korrelierte das Alkoholverlangen positiv mit der Aktivierung der Amygdala während der Annäherung an den Alkohol. Schließlich zeigten Patienten der CBM-Gruppe im Vergleich zu der Placebo-Gruppe größere Abnahmen der Cue-Reaktivität in der bilateralen Amygdala. In der CBM-Gruppe, jedoch nicht in der Placebo-Gruppe, korrelierte die Abnahme des Alkoholverlangens mit der Abnahme der Amygdala-Aktivierung.

Diese Ergebnisse deuten darauf hin, dass der automatische Substanz-Annäherungsbias in verschiedenen substanzabhängigen Populationen vorhanden ist. Der automatische Substanz-Annäherungsbias scheint nach Abstinenz nicht konsistent zu sein, wie es Incentive-Sensitisation-Suchtmodelle nahelegen; vielmehr nimmt er offenbar nach längerer Abstinenz ab. Im Einklang mit solchen Modellen steht jedoch der Befund, dass der automatische Alkoholannäherungsbias bei alkoholabhängigen Patienten mit der Aktivierung mesolimbischer Areale assoziiert ist, die eine Schlüsselrolle bei Belohnungs- und motivationalen Prozessen spielen. CBM kann die Alkohol-Cue-induzierte mesolimbische Hirnaktivierung bei alkoholabhängigen Patienten beeinflussen. Dies könnte ein zugrundeliegender Mechanismus der therapeutischen Effektivität des CBMs und einer erfolgreichen Abstinenz im Allgemeinen sein.

iii. Keywords

Addiction, Alcohol-dependence, Approach bias, Approach Avoidance Task, Cognitive Bias Modification training, Craving, fMRI, Implicit cognition, Neuroimaging, Reward, Smoking, Smoking cessation

iv. Abbreviations

AAT	Approach Avoidance Task
BOLD	Blood-Oxygen-Level Dependent
CBM	Cognitive Bias Modification training
DAQ	Desire for Alcohol Questionnaire
dlPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPI	Echo Planar Imaging
FWE	Family Wise Error
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
NAcc	Nucleus Accumbens
QSU	Questionnaire of Smoking Urges
ROI	Region of Interest
RT	Reaction Time/ Response Time
SRC	Stimulus–Response Compatibility Task
SVC	Small Volume Correction
VTA	Ventral Tegmental Area

v. Original publications

This dissertation is based on the following research articles:

Experiment I

Wiers CE, Kühn S, Javadi AH, Korucuoglu O, Wiers RW, Walter H, Gallinat J, Bermpohl F (2013). Automatic approach bias towards smoking cues is present in smokers but not in ex-smokers. *Psychopharmacology, 229*(1): 187-197. doi: 10.1007/s00213-013-3098-5

The original article is online available at:
http://dx.doi.org/10.1007/s00213-013-3098-5

Experiment II

Wiers CE, Stelzel C, Park SQ, Gawron CK, Ludwig VU, Gutwinski S, Heinz A, Lindenmeyer J, Wiers RW, Walter H[*], Bermpohl F[*] (2014). Neural correlates of alcohol-approach bias in alcohol addiction: the spirit is willing but the flesh is weak for spirits. *Neuropsychopharmacology, 39*(3), 688-697. doi: 10.1038/npp.2013.252

The original article is online available at:
http://dx.doi.org/10.1038/npp.2013.252

Experiment III

Wiers CE, Stelzel C, Gladwin TE, Park SQ, Pawelczack S, Gawron CK, Stuke H, Heinz A, Wiers RW, Rinck M, Lindenmeyer J, Walter H[*], Bermpohl F[*]. Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol-dependence.
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CHAPTER 1
INTRODUCTION

'It is not I who become addicted, it is my body'

Jean Cocteau
(1889-1963)

The quote of Jean Cocteau illustrates a conflict in the understanding of drug addiction: is addiction a social, behavioural problem or is it a purely bodily disease? Whilst in the 19th century drug addiction was seen mainly as a weakness of will, over the last decades the view on drug addiction has been radically changed into a medical issue. Receptors and ligands of drugs of abuse have been identified, neural circuits have been studied in animal models, and neuroimaging studies have revealed neural differences between addicted and non-addicted individuals. These insights all contributed to the vision of addiction as a chronic brain illness (Leshner, 1997).

This thesis is concerned with automatic approach behaviour to drug cues in addiction. Automatic approach tendencies have been shown in drug-addicted individuals and are hypothesized to play a key role in relapse, even after years of abstinence. The thesis investigates the adaptability of drug approach tendencies after long-term abstinence and after behavioural re-training. Using neuroimaging techniques, the neural underpinnings of this psychological phenomenon as well as the neural effects of retraining are investigated. As such, the thesis identifies neurobiological targets of a psychotherapeutic intervention, which has been labelled a form of "neuropsychotherapy" (Walter, Berger, & Schnell, 2009).

1.1 General overview of addiction

Alcohol and tobacco are the most frequently used drugs of abuse in modern western society. Whist most drugs of abuse such as cocaine, heroin and ecstasy are illegal because of significant health risks for the drug-taker, alcohol and tobacco are not (Nutt, King, & Phillips, 2010). Instead, the drugs are widely accepted in society. Regulation of alcohol and nicotine does take place, but on a more subtle basis: through governmental taxes, age restrictions of purchase or the recently introduced smoking ban in public areas. However, despite legality, long-term alcohol and tobacco use can lead to serious mental and physical health problems, including dependence on the drug. Alarmingly, a recent study rated alcohol to be the most harmful drugs of all if societal costs, personal consequences and health risks are considered (Nutt et al., 2010).

World-wide, the use of alcohol and illicit drugs account for 5.4% of annual disease burden, with tobacco use being responsible for 3.7% (WHO, 2010). In Europe, 3.4% of all citizens suffer from an alcohol use disorder (Wittchen et al., 2011) and in Germany alone, the prevalence of daily cigarette smokers over 15 years of age is now 23.2% (WHO, 2009). According the Diagnostic and Statistical Manual of Mental Disorders (DSM) American Psychiatric Association (2001) tobacco or alcohol dependence are diagnosed when a certain set of criteria are met, such as drug tolerance, withdrawal, out of control use and the continuation of the drug despite negative consequences (see Supplement B). Drug-taking despite knowing the risks and likely harmful effects has been described as the "central paradox of addiction" (Stacy & Wiers, 2010). Relapse rates in tobacco and alcohol-dependence have been shown to be very high, and without intervention, rates of around 80-85% have been reported (Heinz, Beck, Grusser, Grace, & Wrase, 2009; Hughes, Peters, & Naud, 2008). Therefore, research investigating psychobiological mechanisms underlying addictive behaviour and relapse is largely needed to improve therapy.

1.2. Theoretical background on biased motivation in addiction

Over the last decades, many psychobiological models have been developed to describe addictive behaviour and its persistence (e.g., Jentsch & Taylor, 1999; Koob & Volkow, 2010; Robbins & Everitt, 1999; Robinson & Berridge, 2003). These models can roughly be divided into motivational models on the one hand and models that propose a "lack of control" to resist temptations to take drugs on the other. The primary theoretical framework of this thesis is formed by the motivational "incentive sensitisation theory" proposed by Robinson and Berridge (1993)

and by dual process models that emphasize the interplay between strong motivational processes and weak control to resist drug-taking.

Central to motivational models is the classical conditioning of motivational reactions to drugs. When people start taking drugs, they take them for various reasons: to get rid of negative feelings (i.e., negative reinforcement), to aim for an enjoyable effect (i.e., positive reinforcement) and, among others, because of peer pressure and genetic vulnerability. However, after repeated drug-use, drug paraphernalia (e.g., the sight of a cigarette, an empty beer bottle) or drug contexts (e.g., a pub) become associated with the effects of the drug (Siegel, 1999). These stimuli become conditioned stimuli (CS) to drug-effects and, as their conditioned response (CR), trigger drug craving or approach-like motivational responses (i.e., "drug cue reactivity"; Heinz et al., 2009; R. W. Wiers et al., 2007).

The central claim of the incentive sensitisation theory (Robinson & Berridge, 1993) is that repeated use of addictive drugs causes "incentive sensitisation": that is, the neural response to drugs found in brain regions related to reinforcement and motivation (see below) becomes enhanced. This neural response causes drug cues associated with this brain response to the drug to acquire "incentive salience": the property of, first, attracting attention and, second, of acting as a "motivational magnet". That is, becoming attractive and evoking approach behaviour. In other terms, drugs and drug cues evoke increasing "wanting" – as distinguished from hedonic impact, or "liking", which may habituate rather than sensitise over time. Stimuli with incentive salience can act as reinforcers. Thus, addiction involves a neural system "programmed" to achieve an inflexible goal - drug-seeking - but that can exploit all the learning mechanisms of the brain to flexibly achieve it (Robbins & Everitt, 1999; Tiffany, 1990).

On a neurobiological level, mesolimbic neuroadaptations are hypothesized to underlie motivational reactions to drugs (Robinson & Berridge, 2003). Alcohol and nicotine, as well as many other drugs of abuse, trigger the release of dopamine from the ventral tegmental area (VTA), which has projections to mesolimbic brain structures such as the nucleus accumbens (NAcc), the medial prefrontal cortex (mPFC), basolateral amygdala as well as prefrontal areas (Heinz et al., 2009; Hyman & Malenka, 2001). Since dopamine signals motivational relevance, with every drag or drink, Pavlovian conditioned associations between drug cues and reward are

formed (Baler & Volkow, 2006; Heinz et al., 2009). In this way dopamine signaling has been hypothesized as a key neurobiological substrate of drug-cue learning, incentive sensitisation and approach-like motivational responses (Robinson & Berridge, 1993, 2003).

The incentive sensitisation theory explains the "bottom-up" aspects of addiction; however, other theories emphasize "top-down" processes that determine whether incentive salience can be regulated. For example, addiction has also been described as a disorder of disrupted self-control over automatically triggered impulses to use (Baler & Volkow, 2006). The dorsolateral prefrontal cortex (dlPFC) particularly has been shown to be structurally and functionally impaired in drug-dependent individuals, making it an important region for the theorized lack of cognitive control in addiction (Baler & Volkow, 2006; Bechara, 2005; Hayashi, Ko, Strafella, & Dagher, 2013; Jentsch & Taylor, 1999; Kalivas, 2004; Park et al., 2010; Volkow et al., 2010). Dual process models of addiction are focused on the interaction between top-down and bottom-up processes. There is a wide variety of such models, some of which posit dual systems - an associative, motivational (or “impulsive”) system in which incentive sensitisation would be located, and a deliberative, reflective system that controls behaviour in order to achieve long-term goals by delaying gratification and inhibiting impulsive behaviour such as drug taking - while others describe different dualities, e.g., between states of processing that bias response selection towards impulsive versus reflective response selection (Bechara, 2005; Gladwin, Figner, Crone, & Wiers, 2011; R. W. Wiers et al., 2007). Despite their differences, dual process models share the common feature of possibly antagonistic interactions between an overactive, motivational system and a less well functioning control system. Together, alterations of dysfunctional processing in these two systems may explain the conflict that typifies addiction: persistent drug taking, even when the individual appears to have an explicit desire to quit.

1.3 Experimental evidence for biased motivation in addiction

Enhanced reactivity to drug-related cues has been repeatedly shown in physiological and behavioural studies among various drug-dependent individuals and is thought to be the underlying mechanism inducing relapse, even after years of abstinence (Heinz et al., 2009). Drug cues have been shown to increase subjective craving and arousal (Carter & Tiffany, 1999), evoke mesocorticolimbic brain activation (Heinz et al., 2009; Schacht, Anton, & Myrick, 2013), capture automatic attention (Field & Cox, 2008) and elicit approach responses (R. W. Wiers et al., 2007).

This paragraph reviews findings regarding explicit ratings of craving, implicit drug biases and neural drug cue reactivity. Open research questions are discussed, leading to the aims of this thesis.

1.3.1 Subjective craving

The most commonly collected measures of drug cue reactivity are self-reported craving questionnaires (Carter & Tiffany, 1999). Cues of alcohol are presented and the respondent can report to what extend this leads to increased craving for the drug (e.g., physical arousal, urges to take the drug, not being able to stop the drug after starting consumption). Alternatively, standardized questionnaires have been developed such as the "Desire for Alcohol Questionnaire" (DAQ; see paragraph 3.2), including state-related questions on drug-thoughts. Although often used, explicit self-reports of craving may be affected by social desirability or a wish to remain abstinent (e.g., "I am in therapy, therefore I cannot crave"). Moreover, craving is a construct that can operate outside of conscious awareness (Berridge & Robinson, 1995). Therefore, it has been questioned whether self-reports are reliable and valid measures of craving (Sayette et al., 2000).

1.3.2 Automatic biases

In the past two decades computerized tasks have been developed that measure automatic biases in drug motivation without explicitly asking participants (see Stacy and Wiers 2010 for a review). These reaction time (RT) tasks are considered implicit or automatic if task instructions are indirect (i.e., participants are largely unaware of the task's outcome measures) or if the outcome measures meet at least one of the following set of properties: being fast, goal-independent, or not directly controllable (De Houwer, 2006; Stacy & Wiers, 2010). Because of these criteria, implicit measures have the advantage of being less susceptible to social desirability than explicit measures (such as subjective craving) and could measure automatic processes that lie outside of conscious awareness (De Houwer, 2006). For example, Huijding and de Jong (2006) provide evidence that implicit measures better predict more automatic aspects of behaviour, whereas explicit measures better estimate controlled behaviour.

In various implicit tasks, substance users have shown automatic selective attention to drug-related as compared to neutral cues (attentional bias) as well as the tendency to approach these cues faster than to avoid them (approach bias), which is typically not seen in control groups. The

attentional bias has been shown in multiple studies in tobacco and alcohol addiction: first, in the addiction Stroop test (W. M. Cox, Fadardi, & Pothos, 2006) tobacco smokers and alcohol-dependent patients have been shown to respond more slowly to drug-related words compared to neutral words, suggesting distraction by drug cues (Drobes, Elibero, & Evans, 2006; Field & Cox, 2008; Field, Mogg, Mann, Bennett, & Bradley, 2013; Munafo, Johnstone, & Mackintosh, 2005; Munafo, Mogg, Roberts, Bradley, & Murphy, 2003; Waters, Shiffman, Sayette, et al., 2003). Second, in visual cue tasks, two pictures appear simultaneously on a screen, followed by a probe to which participants are instructed to react. The probe follows either a drug-related cue or a neutral cue and tobacco and alcohol-dependent individuals have been shown to fixate longer on tobacco/alcohol cues than neutral cues (e.g., Bradley, Field, Healy, & Mogg, 2008; Chanon, Sours, & Boettiger, 2010; Field et al., 2013; Mogg, Bradley, Field, & De Houwer, 2003; Munafo et al., 2005; Waters, Shiffman, Bradley, & Mogg, 2003; but see Townshend & Duka, 2007).

Few studies have concentrated on automatic action tendencies elicited by drug cues. In the Stimulus–Response Compatibility (SRC) task, participants move a manikin towards (approach) and away from cues (avoidance) with button presses (i.e., arrow pointing up/down) on a computer screen. Smokers have been shown to move the manikin faster towards smoking cues than towards neutral cues and, hence, reveal a smoking approach bias (Bradley et al., 2008; Bradley, Field, Mogg, & De Houwer, 2004; Mogg et al., 2003; Mogg, Field, & Bradley, 2005; Thewissen, Havermans, Geschwind, van den Hout, & Jansen, 2007). However, one study in alcohol-dependent patients did not demonstrate an approach bias on the SRC (Barkby, Dickson, Roper, & Field, 2012).

A second task that can measure automatic approach tendencies is the Approach Avoidance Task (AAT), which is the task used for assessing the drug approach bias in this thesis. Participants push and pull pictorial cues (drug-related or neutral) with a joystick in response to the content-irrelevant format of the cue (landscape or portrait; see paragraph 3.1.1 for details of the task). Cues are either drug-related or neutral, and heavy drinkers (R. W. Wiers, Rinck, Dictus, & van den Wildenberg, 2009), alcohol-dependent patients (Ernst et al., 2012; C. E. Wiers et al., 2014; R. W. Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011), heroin abusers (Zhou et al., 2012) and heavy cannabis users (Cousijn, Goudriaan, & Wiers, 2011) have been shown to faster approach than avoid drug cues compared to non-addicted control groups. The AAT has at least

two benefits over the SRC: first, movements of participants are accompanied by a visual zooming function: pictures increase and decrease in size upon an approach movement (pulling a joystick) or an avoidance movement (pushing a joystick) respectively. In this way, the combination of pull/push movements with visual feedback during AAT better resembles the approach and avoid tendencies towards and away from oneself than the upward and downward movements on the SRC (Krieglmeyer & Deutsch, 2010). Second, whereas in the SRC participants are explicitly instructed to move the manikin towards or away from drug-related or drug-unrelated stimuli in separate blocks, the AAT makes use of instructions concerning irrelevant features. That is, participants are asked to respond to a feature that is irrelevant to the task, namely the format instead of content of the stimuli. As such, the AAT is relatively implicit in both outcome measure and instruction, which makes it more likely to measure automatic processes (De Houwer, 2003).

Both the attentional and the approach bias have been associated with motivational measures of drug use and clinical measures. For example, there is an accumulation of evidence that both smokers' attentional bias and approach bias for cigarettes correlate positively with explicit craving scores (Mogg et al., 2003; Mogg et al., 2005; Waters, Shiffman, Bradley, et al., 2003; Watson, de Wit, Cousijn, Hommel, & Wiers, 2013), predict relapse (Janes, Pizzagalli, Richardt, de, et al., 2010; Waters, Shiffman, Sayette, et al., 2003) and smoking behaviour (Waters & Feyerabend, 2000). In alcohol-dependent inpatients, the approach bias was correlated with drinking consumption before treatment as well as self-reported alcohol approach preferences (Barkby et al., 2012). These findings highlight the clinical importance of automatic biases in drug addiction.

1.3.3 Neural drug cue reactivity

Due to technological inventions it has become possible to investigate the structure and functioning of the human brain in vivo. These techniques, especially the non-invasive technique of functional magnetic resonance imaging (fMRI), have led to an accumulation of neurobiological findings that can be used for therapeutic purposes. Since the 1990s the blood-oxygen-level dependent (BOLD) signal has been used to indirectly measure brain activity. A standard paradigm in drug addiction is the cue reactivity paradigm: the passive viewing of drug cues. In these paradigms, it has been shown that BOLD activation in mesocorticolimbic structures is increased in drug-users as compared to non-addicted individuals (for a review in

alcohol addiction: Heinz et al., 2009; for meta-analyses: Kuhn and Gallinat, 2011; Schacht et al., 2013). Key brain areas that have been shown to be activated in drug-users in cue reactivity paradigms are the NAcc, mPFC, basolateral amygdala, and the dlPFC. The NAcc, mPFC and amygdala have been associated with bottom-up motivational aspects of cue reactivity (Braus et al., 2001; Hare, Camerer, & Rangel, 2009; Heinz et al., 2009; Wrase et al., 2007), reward processing (Heekeren et al., 2007; Kahnt, Heinzle, Park, & Haynes, 2010; Koob & Volkow, 2010), subjective drug craving and relapse (Beck et al., 2012; Childress et al., 1999; Grusser et al., 2004; Hayashi et al., 2013; Heinz et al., 2004; Volkow, Fowler, & Wang, 2004). Moreover, the amygdala plays an important role in the emotional salience of drug stimuli and Pavlovian conditioned learning (Heinz et al., 2009; Schneider et al., 2001). In contrast, the dlPFC has been shown to play an important role top-down control over motivational reactions to drug cues in addiction (Baler & Volkow, 2006; Bechara, 2005; Hayashi et al., 2013; Jentsch & Taylor, 1999; Kalivas, 2004; Park et al., 2010; Volkow et al., 2010).

Despite robust findings of mesocorticomlimbic areas in cue reactivity, the exact functions of individual areas (e.g., attention, explicit craving, automatic action tendencies or cognitive control) remain poorly understood. Studying attentional or approach bias paradigms with fMRI may hence disentangle specific roles of these areas in automatic processes. So far, fMRI studies using attentional bias paradigms (e.g., visual probe task, attentional bias line counting task) have found increased activity in a mesocorticolimbic network to be associated with increased attentional bias in drug-users, involving the NAcc, hippocampus, mPFC, anterior cingulate cortex, insula and temporal regions (middle and superior temporal gyrus; Janes, Pizzagalli, Richardt, Frederick et al., 2010; Luijten et al., 2011; Nikolaou, Field, Critchley, & Duka, 2013; Vollstadt-Klein et al., 2012). To date, two fMRI experiments studying the neural correlates of approach/avoidance behaviour on the AAT have been published, both in the area of emotional processing. In these studies, participants pulled (approach) and pushed (avoid) pictures of happy and sad faces with a joystick. It was found that the dlPFC was more active when stimulus and response were incongruent (i.e., for avoiding happy and approaching sad faces), than during congruent trials (Roelofs, Minelli, Mars, van Peer, & Toni, 2009; Volman, Toni, Verhagen, & Roelofs, 2011). Moreover, Derntl et al. (2011) demonstrated that the amygdala is activated when subjects approach happy faces. The only published approach/avoidance fMRI study (using the SRC) related to addiction (Cousijn et al., 2012) did not find direct neural differences in

approaching cannabis versus neutral cues in heavy cannabis users. However, the authors did show a main effect of increased mPFC activity in both cannabis users and controls for approaching versus avoiding cues. Moreover, weaker approach bias-related activation in dlPFC was associated with larger cannabis consumption 6 months later. Furthermore, Ernst et al. (2012) used near-infrared spectroscopy (NIRS) to study approach/avoidance tendencies in alcohol-dependent patients on the AAT. The study of Ernst et al. indicated that the orbitofrontal cortex (OFC) is more active when alcohol-dependent patients approach alcohol cues than when they avoid alcohol cues. However, it should be noted that NIRS is limited to examining cortical structures and the spatial resolution of the method is rather poor. Hence, a combination of the AAT and fMRI should be a valid method for disentangling cortical as well as subcortical structures involved in approach and avoid behaviour in addiction. Currently, however, the neural basis of the drug approach bias remains an open area of research.

1.4 Can biased motivation be changed?

According to the incentive sensitisation model of Robinson and Berridge (1993), sensitisation to drug cues is largely permanent and serves a causal role in automatic approach tendencies and relapse. Dual process models of addiction also suggest that drug-seeking tendencies remain, but emphasize that successfully refraining from a drug requires the ability and willingness to control these tendencies (R. W. Wiers et al., 2007).

Only few studies have investigated whether biased drug motivation can be affected by abstinence or therapy. In this paragraph, I first describe theoretical and empirical insight into the effect of abstinence on automatic biases to drug cues. The second paragraph describes how a cognitive bias modification (CBM) training scheme, that has the goal to selectively unlearn automatic biases, can influence automatic biases and potentially neural functioning.

1.4.1 Abstinence

How persistent is the automatic approach bias after abstinence? There is first evidence that immediate smoking abstinence increases reinforcing properties of smoking and attentional bias for smoking words (Waters & Feyerabend, 2000), whereas after two weeks of cessation smoking reinforcement (Lussier, Higgins, & Badger, 2005), craving, and withdrawal symptoms (Yoon, Higgins, Bradstreet, Badger, & Thomas, 2009) decline. In alcohol-dependent patients who were

abstinent for longer than two weeks, abstinence and attentional bias correlated negatively, indicating disengagement of attention to drug cues after abstinence (Vollstadt-Klein, Loeber, von der Goltz, Mann, & Kiefer, 2009). Various studies on smoking cessation techniques have used attentional bias (but not approach bias) as an outcome measure, with conflicting results. On the one hand, smokers have been shown to be able to decrease motivational cue reactivity by cognitive strategies such as cognitive reappraisal (Littel & Franken, 2011). On the other hand, Pavlovian extinction training – in which drug cues are presented to smokers but remain unreinforced – have been shown to decrease craving but not attentional bias in smokers (Kamboj et al., 2012). Overall, these studies provide first evidence that it is possible to decrease automatic biases, although the mechanisms behind this are poorly understood and direct evidence for the approach bias is lacking.

Studies measuring automatic biases in former drug users that have been abstinent for a long time are scarce and provide contradictory results. Munafo et al. (2003) found that ex-smokers who had been abstinent for longer than four years, demonstrated diminished attentional bias for smoking cues, suggesting that biases can fade away. Nevertheless, other studies with a similar design did not find direct RT differences between ex-smokers and smokers (Munafo & Johnstone, 2008; Munafo et al., 2005; Nestor, McCabe, Jones, Clancy, & Garavan, 2011). Interestingly, Nestor et al. found that smokers have increased mesolimbic brain activity while watching smoking cues compared to ex-smokers, whereas prefrontal areas were more active in ex-smokers. Since these brain areas are involved in reward and cognitive control respectively, this suggests that cue reactivity decreases after cessation, parallel to increased cognitive control. To date, no studies have investigated approach tendencies after long-term drug cessation.

1.4.2 Cognitive Bias Modification training

The computerized tasks that are used to assess automatic biases have been adapted into CBM training schemes with the goal to re-train automatic biases. The first study investigating CBM adapted a visual probe task for anxiety (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002), in which probes follow neutral cues in the majority of cases, therefore disengaging attention from anxious cues and reducing attentional bias. CBM has repeatedly been shown to reduce attentional bias in anxiety, although with small effects, as recently found in a meta-analysis (Hallion & Ruscio, 2011). Attentional biases for smoking and alcohol have been shown

to be modifiable with a dot probe-based CBM training in smokers (Attwood, O'Sullivan, Leonards, Mackintosh, & Munafo, 2008; Field, Duka, Tyler, & Schoenmakers, 2009), heavy drinkers (Fadardi & Cox, 2009; Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007) and alcohol-dependent inpatients (Schoenmakers et al., 2010). Importantly, some studies found generalization to new stimuli (Fadardi & Cox, 2009; Schoenmakers et al., 2010). However, others did not find generalization after one session of training (Field et al., 2009; Schoenmakers et al., 2007)

Recently, the AAT has also been adapted into a CBM, in which patients systematically but implicitly push away alcohol cues with a joystick to decrease the drug approach bias. In heavy drinking students, CBM training has been shown to decrease the strength of the approach bias and reduce post-training alcohol intake in successfully trained participants (R. W. Wiers, Rinck, Kordts, Houben, & Strack, 2010). Moreover, in two recent randomized-controlled trials CBM reduced relapse rates up to 13% in alcohol-dependent patients, compared to a placebo-training group (R. W. Wiers et al., 2011) and compared to a non-training group (Eberl et al., 2013). This shows the clinical potential of CBM in addiction. However, it is as yet unclear how CBM affects brain function. For instance, CBM could directly reduce the incentive salience of alcohol cues (R. W. Wiers, Gladwin, & Rinck, 2013). This is an important question to answer to understand the mechanisms of CBM and hence to further enhance its efficacy and improve addiction treatment.

1.5 Aims of the thesis

The aims of this thesis are to investigate (1) whether drug users have an automatic approach bias for drug cues on the AAT and whether this bias is related to drug craving; (2) whether the automatic approach bias persists after long-term drug abstinence; (3) the underlying neural correlates of the drug approach bias; and (4) the neural effects of CBM on drug cue reactivity.

In the next chapter, these aims are formulated into the general research questions central to this thesis. The respective hypotheses are outlined. In chapter 3 the methodology of the three empirical studies are described, followed by a summary of the studies in chapter 4. Chapter 5 discusses the main findings of the studies in light of incentive sensitisation and dual process models of addiction. Study findings are integrated into a psychobiological model of addiction,

based on incentive salience and dual process models. Finally, study limitations and future research directions are discussed.

CHAPTER 2
RESEARCH QUESTIONS AND HYPOTHESES

The main aim of this thesis is to empirically investigate the automatic approach bias to drug cues, its neural underpinnings and the neural effects of CBM. The three experiments that form the body of this thesis (C. E. Wiers et al., 2013; C. E. Wiers et al., 2014; C. E. Wiers et al., under review) aimed to answer four research questions. These general questions and the respective hypotheses specific to our empirical studies are listed in this chapter.

2.1 Research questions

This thesis investigates the following four research questions:

First question: Do drug users have an automatic approach bias for drug cues on the AAT? Is the strength of this bias related to drug craving?
Experiment I and II

Second question: Do former drug users still show an automatic approach bias to drug cues after long-term abstinence?
Experiment I

Third question: What are the neural correlates underlying the drug approach bias in drug-addicted individuals? Are these correlates related to subjective drug craving?
Experiment II

Fourth question: What are the effects of CBM on neural drug cue reactivity in drug-dependence? Are these neural effects related to effects of CBM on drug craving?
Experiment III

2.2 Hypotheses

First question: Do drug users have an automatic approach bias for drug cues on the AAT? Is the strength of this bias related to drug craving?

Experiment I and II

As has been summarized in the previous chapter, there is empirical evidence for a drug approach bias on the AAT in various drug users (i.e., heavy drinkers, alcohol-dependent patients and heroin- and cannabis abusers). However, it remains as yet unknown whether heavy cigarette smokers also reveal this automatic bias for smoking cues.

Smokers have shown increased attentional and approach bias for smoking cues on the drug Stroop task, visual probe task and SRC (see paragraph 1.3.2). Following the incentive sensitisation theory of addiction that suggests a common underlying mechanism of attentional and approach bias in drug-dependence (Robinson & Berridge, 1993, 2003), we expected that heavy smokers would show an automatic bias for smoking cues on the AAT compared to a never-smoking control group. Further, we hypothesized that we would replicate the behavioural alcohol approach bias in alcohol patients compared to a non-addicted control group (Ernst et al., 2012)

Since automatic biases have been associated with craving scores (see 1.3.2), we hypothesized that the strength of the automatic drug approach bias would be positively correlated with drug craving, in smokers and alcohol-dependent patients.

Second question: Do former drug users still show an automatic approach bias to drug cues after long-term abstinence? *Experiment I*

There is a scarcity of studies investigating the course of automatic biases after drug cessation. According to the incentive sensitisation model (Robinson & Berridge, 1993, 2003), sensitisation to drugs is thought to be (semi-)permanent, which could imply that they serve a causal role in relapse. Dual process models of addiction add to this model that successfully refraining from a drug also requires the ability and willingness to control motivational drug-seeking tendencies (R. W. Wiers et al., 2007).

As summarized in paragraph 1.4.1, the evidence for (diminished) automatic biases in former drug users is scarce and results are conflicting. Nevertheless, some studies suggest salience for cues to

decrease over abstinence (Munafo et al., 2003; Nestor et al., 2011), which lead to the hypothesis that the automatic drug approach bias would be reduced in former drug users after long-term abstinence compared to current drug users.

Third question: What are the neural correlates underlying the drug approach bias in drug-addicted individuals? Are these correlates related to subjective drug craving? *Experiment II*

Although the alcohol approach bias in alcohol-dependent patients is a well-studied psychological phenomenon, relatively little is known about its underlying neural correlates. The incentive sensitisation theory of addiction suggests mesocorticolimbic neuroadaptations to underlie the drug approach bias (Robinson & Berridge, 2003). As summarized in the introduction, key areas of a bottom-up motivational system activated in drug cue reactivity designs are the NAcc, mPFC and amygdala (Beck et al., 2012; Braus et al., 2001; Childress et al., 1999; Grusser et al., 2004; Hare et al., 2009; Hayashi et al., 2013; Heinz et al., 2009; Heinz et al., 2004; Schacht et al., 2013; Volkow et al., 2004; Wrase et al., 2007). In contrast, the dlPFC has been related to suboptimal cognitive control of drug-related motivation in addiction (Baler & Volkow, 2006; Bechara, 2005; Hayashi et al., 2013; Jentsch & Taylor, 1999; Park et al., 2010).

We hypothesized increased activity in the motivational system (i.e., NAcc, mPFC and amygdala) when patients approach versus avoid alcohol cues. Activations in these areas were expected to correlate with subjective alcohol craving. We expected the dlPFC to be either more or less active while avoiding alcohol cues in patients versus controls, indicating enhanced or reduced inhibitory control respectively. Following previous approach/avoidance studies on emotional processing that found dlPFC activity when stimulus and response are incongruent (Roelofs et al., 2009; Volman et al., 2011), the dlPFC would be expected to be active in patients while avoiding alcohol cues. Alternatively, when following the hypothesis that patients lack the control to avoid alcohol cues, decreased dlPFC activation for avoiding alcohol cues would be expected.

Fourth question: What are the effects of CBM on neural drug cue reactivity in drug-dependence? Are these neural effects related to effects of CBM on drug craving? *Experiment III*

As summarized in the introduction, neuroimaging studies have shown that when alcohol-dependent patients are exposed to alcohol cues this evokes activation of mesolimbic brain areas related to craving (Myrick et al., 2004; C. E. Wiers et al., 2014), reward processing (Heekeren et al., 2007; Koob & Volkow, 2010; Park, Kahnt, Rieskamp, & Heekeren, 2011) and to alcohol consumption after relapse (Beck et al., 2010; Beck et al., 2012; Grusser et al., 2004). Although cue reactivity has been hypothesized to be sustained after years of abstinence (Robinson & Berridge, 1993, 2003), studies suggest that behavioural and/or pharmacological therapy of only a few weeks can decrease cue-evoked activation in the NAcc (Myrick et al., 2010; Vollstadt-Klein et al., 2011) and amygdala (Schneider et al., 2001) in alcohol-dependent patients.

Two recent randomized-controlled experiments showed that a three-week CBM training reduced the automatic alcohol approach bias as well as relapse rates in alcohol-dependent patients, compared to a placebo-training group (R. W. Wiers et al., 2011) and compared to a non-training group (Eberl et al., 2013). However, it is as yet unclear how CBM affects brain function, which is the fourth question of this thesis. For instance, CBM could directly reduce the incentive salience of alcohol cues as proposed by R. W. Wiers et al. (2013).

In studying the neural effects of CBM on alcohol cue reactivity, we first expected to replicate the reduction of the strength of the behavioural alcohol approach bias in alcohol-dependence after a CBM training of three weeks. Second, we expected drug-cue evoked activations to decrease after CBM training in the amygdala and NAcc. Third, decreases of activations in these brain areas were expected to covary with changes in craving.

In sum, the empirical studies in this thesis investigated the automatic drug approach bias in cigarette smokers (experiment I) and alcohol-dependent patients (experiment II), its persistence after prolonged abstinence in ex-smokers (experiment I), its neural mechanisms in alcohol-dependent patients (experiment II), its relation to drug craving (all experiments) and the neural effects of CBM on drug cue reactivity (experiment III). The studies may hence provide insight in underlying processes of the drug approach bias, and may be particularly valuable for future treatment of drug-addicted individuals.

CHAPTER 3
GENERAL METHODOLOGY

In this chapter, the methodology of the three empirical studies that constitute this thesis (C. E. Wiers et al., 2013; C. E. Wiers et al., 2014; C. E. Wiers et al., under review) are briefly described. The task central to all three studies was the implicit AAT: as a behavioural measure in all experiments, adapted for fMRI in experiment II and adapted into CBM training in experiment III.

First, I will describe the task structure of the AAT, the CBM training and placebo tasks, the fMRI alcohol cue reactivity task and the picture rating scales used. Second, a list is given of the most important questionnaires, for example for assessing drug craving, and diagnostic interviews used in the studies. Third, details of fMRI parameters are provided as well as main statistical analyses.

3.1 Experimental tasks

3.1.1 Approach Avoidance Task

The AAT was used to measure implicit drug approach biases. The task required participants to push or pull on a joystick in response to an irrelevant feature, namely the format of the cue (landscape or portrait). This irrelevant feature instruction made the AAT relatively implicit in both outcome measure as well as instruction, making it likely to assess automatic processes (De Houwer, 2003). Approach tendency scores were calculated by the RT difference between pushing and pulling cues (see statistical analyses, paragraph 3.3). Figure 1 depicts an example trial of the AAT.

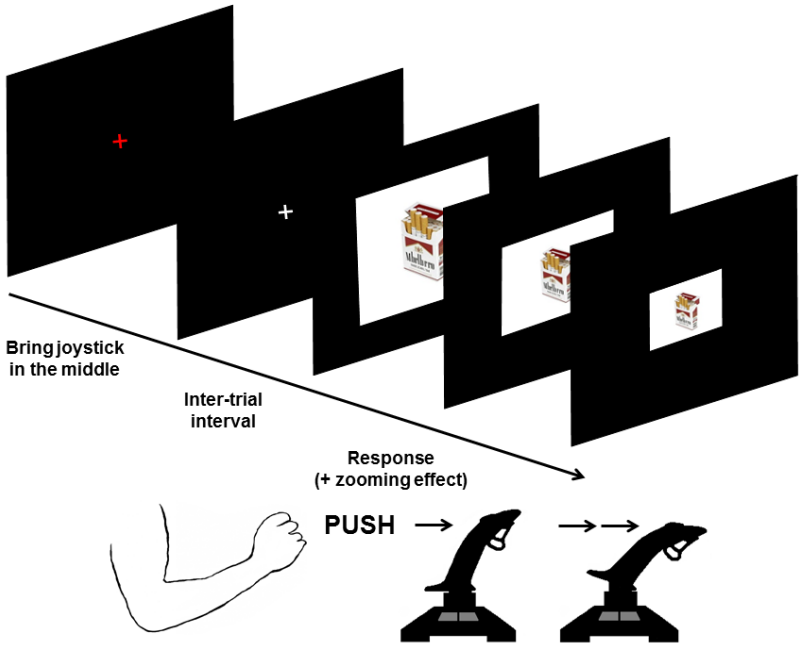

Figure 1. Schematic overview of an avoid alcohol trial on the Approach Avoidance Task (AAT), in which the cue zooms out while pushing on the joystick.

Picture format to response assignment was counterbalanced, with half of the participants pulling the joystick for landscape and pushing it for portrait cues, and vice versa. For optimal approach and avoidance resemblance (Rinck and Becker, 2007), the AAT was developed with a zooming feature; i.e. pulling and pushing the joystick increased and decreased the size of the cue respectively. After practice trials, cues were presented pseudo-randomly over the experiment, maximally allowing three cues with similar content or format in a row. For details on cue contents, number of cues, software of presentation and number of trials used in each study, see the original articles in Supplement A.

3.1.2 Cognitive Bias Modification Training

The Cognitive Bias Modification (CBM) Training was performed in experiment III to re-train automatic approach tendencies to drug cues. The training was an adapted version of the AAT, as was used in previous CBM training studies in alcohol-dependence (Eberl et al., 2013; R. W. Wiers et al., 2011). The training consisted of 6 sessions of 400 trials (approximately 15 minutes per session), presented over 3 weeks (i.e., two sessions per week). The task was comparable to the AAT, in that approach/avoid responses were given according to an irrelevant feature, namely

the format of the cue (landscape/portrait or vice-versa). There were however two versions of the task, which were randomly assigned over alcohol-dependent patients: the CBM group pushed away alcohol in 90% of the cases and pulled alcohol in 10%, whereas this ratio was 50% in the placebo group. The latter, placebo task thus used the same ratio as an assessment AAT. In both trainings, 20 pictures were used (10 containing alcohol beverages and 10 with softdrinks; see also (Eberl et al., 2013; R. W. Wiers et al., 2011). Pictures were not identical to the pictures used in the pre- and post-AAT, to test for generalized training effects based on categories (alcohol/softdrink) rather than on specific pictures. CBM was performed in the Salus Clinic in Lindow, where CBM is a standard treatment.

3.1.3 fMRI cue reactivity

For experiment III, a blocked design fMRI cue reactivity task was designed. The same pictures were presented as in the AAT, namely 40 alcohol cues and 40 softdrink cues. Each block consisted of five stimuli, each presented for 4 seconds, resulting in 8 blocks per category, 16 blocks in total. To observe whether patients were attentive, four blocks were added containing an oddball: a picture with an animal. In these cases, participants had to press a button with their right index finger. Duration of the task was approximately 6 minutes.

3.2 Questionnaires and screening instruments

This section lists the most important questionnaires and screening instruments used in the three studies. Between brackets is reported in which studies the instrument was used.

3.2.1 Drug craving questionnaires

- *Questionnaire of Smoking Urges* (QSU brief; L. S. Cox, Tiffany, & Christen, 2001) to assess tobacco craving. The questionnaire distinguishes two subscales: strong desire to smoke and relief from negative effects. (Used in experiment I)
- *Desire for Alcohol Questionnaire* (DAQ; Love, James, & Willner, 1998) for alcohol craving scores. (Used in experiment II and III)

3.2.2 Diagnostic interview

- *M.I.N.I. plus*, International Neuropsychiatric Interview, German translation (Sheehan et al., 1998). (Used in all experiments; exclusion criteria for alcohol-dependent patients in

experiment II and III were axis I psychiatric disorders according to DSM-IV criteria other than alcohol dependence. For all other participants, a history of axis I or II disorders led to exclusion of participation).

3.3 Scanning parameters and regions of interest

3.3.1 Scanning parameters

Scanning parameters for the AAT (experiment II) and cue reactivity task (experiment III) were identical.

A 3 Tesla whole-body MRI scanner (MAGNETOM Trio, TIM-Technology; Siemens, Erlangen, Germany) was used, equipped with a 12-channel head coil. Standard T2- weighted echo planar imaging (EPI) sequence was used with the following parameters: sequential descending, repetition time 2s, echo time 25 ms, flip angle α=80˚, 64×64 pixels in-plane resolution, 34 slices, slice thickness 3 mm, voxel dimensions 3×3×3 mm^3, a .75 mm gap between slides, field of view 192×192 mm^2. For optimal sensitivity in frontal areas, the acquisition was tilted 25 degrees clockwise from anterior-posterior commissure (Deichmann, Gottfried, Hutton, & Turner, 2003).

All functional data analyses were performed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Data were preprocessed (spatially realigned, slice-time corrected, normalized to the standard Montreal Neurological Institute (MNI) EPI template and smoothed with an 8 mm full width at half-maximum Gaussian kernel). Participants who moved more than 2 mm within runs were excluded.

3.3.2 Regions of interest

In experiment II, four Regions of Interest (ROIs) were created, based on our a-priori hypotheses, as described in chapter 2. For the motivational system, ROIs were the bilateral NAcc and amygdala and mPFC (depicted in red in Figure 2). The ROI relevant for the cognitive control system was the bilateral dlPFC (depicted in blue in Figure 2). In experiment III, ROIs for limbic cue-induced activation and limbic reductions after CBM training were the NAcc and amygdala.

ROIs of the NAcc and amygdala were defined by the bilateral NAcc and amygdala using the human anatomical WFU Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). Since mPFC and bilateral dlPFC are anatomically not clearly defined, two functional ROIs of these brain areas were downloaded from an online atlas of functional ROIs (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012).

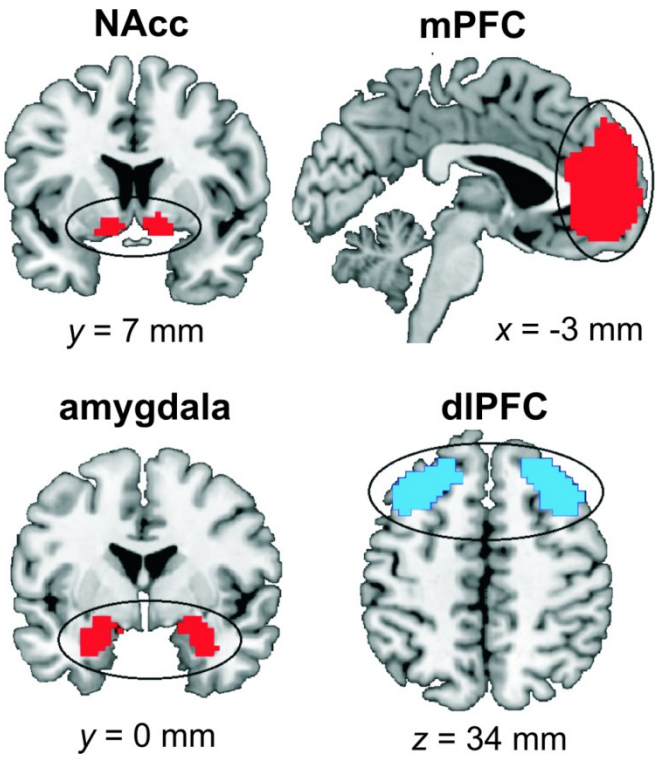

Figure 2. Regions of interests of the motivational system (NAcc, mPFC, amygdala) and of the cognitive control system (dlPFC) shown in red and blue respectively.

3.3 Statistical analyses

For behavioural AAT measures, responses that were missed or incorrect and response times (RTs) longer than 3 standard deviations (SDs) above the mean were discarded based on each participant's performance. Approach tendency scores were calculated by the RT difference between pushing and pulling cues, separately for drug-related and neutral cues. The approach bias was calculated as the difference score of drug and neutral approach tendencies: (drug push – pull) – (neutral push – pull). Approach tendency scores were compared between groups in experiment I and II, and over time (experiment III) with mixed ANOVAs, using SPSS software.

Pearson's correlations were calculated of craving scores with drug approach tendency scores/ drug approach bias scores, in all three experiments.

For neuroimaging, the critical contrast regarding the alcohol approach bias in experiment II was defined as: (approach alcohol – avoid alcohol) – (approach softdrink – avoid softdrink). The reverse, avoid alcohol contrast was defined as: (avoid alcohol – approach alcohol) – (avoid softdrink – approach softdrink). In experiment III, the alcohol cue reactivity contrast was: (alcohol cues – softdrink cues). Moreover, to assess change in alcohol cue reactivity over time the following contrast was built: (alcohol – softdrink pre training) – (alcohol – softdrink post training). Craving scores were correlated with alcohol approach bias-related brain activations (experiment I) and with alcohol cue reactivity (experiment II), by performing regression analyses on these contrast in SPM, with craving scores as a regressor.

All significant levels used were thresholded with $p < .05$. Results with $p < .1$ were reported as trends. For neuroimaging results, all ROIs were used for small-volume correction (SVC), with a significance threshold of $p < .05$, family wise error (FWE)-corrected.

CHAPTER 4
EXPERIMENTS

In this chapter I briefly summarize the three empirical studies that form the main body of the thesis (C. E. Wiers et al., 2013; C. E. Wiers et al., 2014; C. E. Wiers et al., under review). Please refer to Supplement A of this thesis for the complete research articles.

4.1 Experiment I: Automatic approach bias towards smoking cues is present in smokers but not in ex-smokers

Approach tendencies towards drug cues on the AAT have been found in alcohol-dependence (Ernst et al., 2012; C. E. Wiers et al., 2014; R. W. Wiers et al., 2011), heroin addiction (Zhou et al., 2012) and cannabis dependence (Cousijn et al., 2011). However, little is known about the drug approach bias on the AAT in tobacco smokers. Although incentive sensitisation models of addiction hypothesize drug approach tendencies to be relatively permanent over life and to play a large role in relapse, no studies have investigated whether the drug approach bias remains after long-term abstinence.

Therefore the aims of this behavioural study were twofold: first, we investigated the automatic approach bias to smoking cues in heavy tobacco smokers versus never-smokers and studied its relation to tobacco craving. Second, we compared the smoking approach bias of heavy smokers with bias scores of abstinent heavy smokers.

Three groups were included in the experiment: (1) a group of current heavy smokers (n = 24), who smoked more than 15 cigarettes per day; (2) ex-smokers (n = 20), who used to smoke more than 15 cigarettes per day and had been abstinent for at least 5 years at the time of testing; and (3) a group of never-smokers (n = 20), who smoked less than 3 cigarettes in their life. The three groups were matched for age, gender and education. All participants performed the smoking AAT (for details see paragraph 3.1.1), in which participants were instructed to respond to pictures of smoking and neutral cues by pulling (approach) or pushing (avoid) on a joystick, according to the content-irrelevant format of the picture (landscape or portrait). Craving scores were examined using the QSU (see paragraph 3.2).

Heavy smokers demonstrated an automatic approach bias for smoking cues relative to neutral cues, as compared to ex-smokers and never-smokers. In smokers, the strength of the approach tendency for smoking cues was positively correlated with DAQ craving scores. There were no group differences in approach bias scores for ex-smokers and never-smokers, suggesting action tendencies to smoking cues was not present in these groups. Figure 3 depicts bar plots of the behavioural approach tendency scores of all three groups.

These results suggest that approach biases for smoking cues are present in heavy smokers and are diminished after long-term successful smoking cessation. Incentive salience for drug cues may therefore diminish after long-term drug abstinence. In chapter 5 these data will be discussed in light of incentive sensitisation and dual process models of addiction.

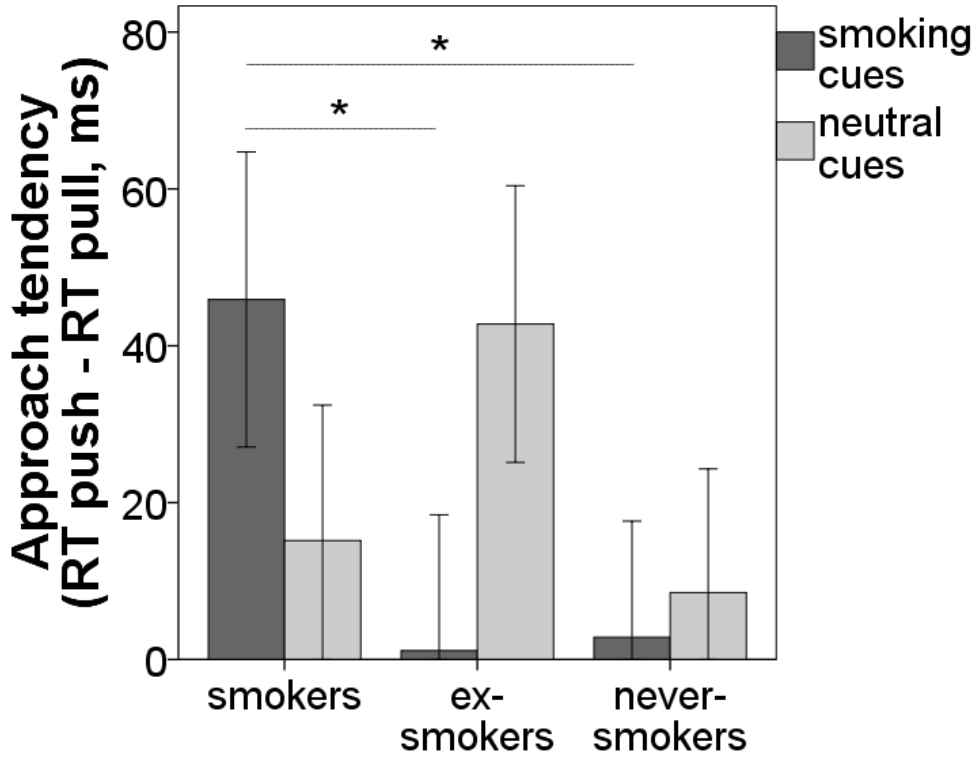

Figure 3. Mean approach tendency score for smoking and neutral cues in smokers, ex-smokers, and never-smokers. Positive scores show faster tendencies to approach than avoid cues. There was a significant interaction effect of picture type × group ($p<.05$). Post-hoc t-tests revealed that tendencies for smoking cues were larger in smokers compared to never-smokers, and compared to ex-smokers (both $p<.05$). Error bars depict 1 standard error (SE) above and below the mean.

4.2 Experiment II: Neural correlates of alcohol-approach bias in alcohol addiction: The spirit is willing but the flesh is weak for spirits

An automatic approach bias for alcohol cues in alcohol-dependent patients has been previously found in behavioural studies (Ernst et al., 2012; R. W. Wiers et al., 2011). However, the underlying brain mechanisms related to the bias remain unknown. In this study we therefore investigated the neural correlates underlying the alcohol approach bias by means of fMRI. Specifically, it was examined whether the alcohol approach bias was due to an overactive motivational system (NAcc, mPFC, amygdala) or a suboptimal control system (dlPFC).

Twenty recently abstinent male alcohol-dependent inpatients took part in the study, as well as 17 healthy age- and education-matched control subjects. All participants performed the AAT (see paragraph 3.1.1 for details on the task) in a 3 Tesla fMRI scanner (see 3.3.1 for scanning parameters). Cues of alcohol beverages and softdrink beverages were pushed and pulled with an MRI-compatible joystick.

Behavioural approach tendencies were calculated for alcohol and softdrinks separately, by subtracting RTs for pushing stimuli minus RTs for pulling stimuli. The behavioural approach bias was defined by approach tendencies for alcohol cues minus approach tendencies for neutral cues. Similarly, for fMRI, the critical contrast regarding the alcohol approach bias was defined as (approach alcohol – avoid alcohol) – (approach softdrink – avoid softdrink). This was reversed for the avoid alcohol contrast: (avoid alcohol – approach alcohol) – (avoid softdrink – approach softdrink). Craving scores were assessed with the DAQ. As described in the methods section 3.3.2, a ROI approach was used for regions interpretable as part of brain areas related to motivational processes (NAcc, mPFC and amygdala) and the dlPFC, related to cognitive control.

In comparison with healthy controls, alcohol-dependent patients had stronger behavioural approach tendencies for alcohol cues than for softdrink cues (Figure 4). In other words, there was a significant difference in the alcohol approach bias between groups. Moreover, patients reported higher DAQ alcohol craving compared to controls. In the approach alcohol fMRI contrast patients showed BOLD responses in the NAcc (Figure 5, panel A) and mPFC (Figure 5, panel B), regions involved in reward and motivational processing (Grusser et al., 2004; Hare et al., 2009; Heekeren et al., 2007; Heinz et al., 2009; Kahnt et al., 2010; Park et

al., 2011). In alcohol-dependent patients, alcohol craving scores were positively correlated with activity in the amygdala for the approach alcohol contrast (Figure 6). The dlPFC was neither activated in the avoid alcohol contrast, nor in the approach alcohol contrast in patients versus controls.

Our data suggest that brain regions that play a key role in reward and motivation are associated with the automatic alcohol approach bias in alcohol-dependent patients. Moreover, patients' subjective craving scores correlated with alcohol approach bias-related amygdala activation. The amygdala has been associated with drug craving in drug cue reactivity studies (Childress et al., 1999; Koob & Volkow, 2010) and with the attribution of motivational salience to rewarding cues (Cunningham & Brosch, 2012; Cunningham, Van Bavel, & Johnsen, 2008; Mahler & Berridge, 2009). We, however, did not find evidence for either more or less inhibitory control by not finding support for dlPFC acitivty in our contrasts. Chapter 5 discusses the current data and provides future research directions as well as limitations of the experiment.

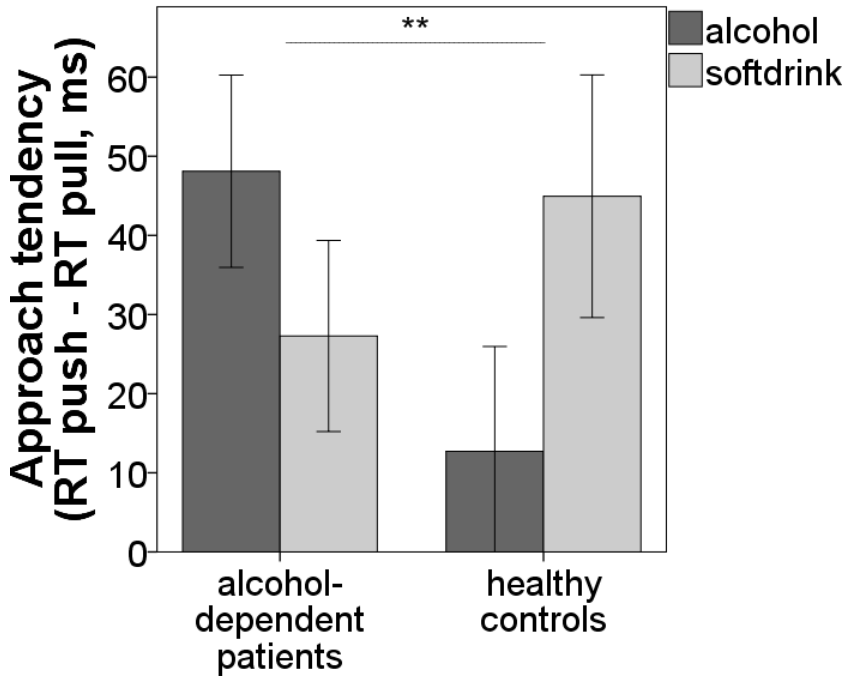

Figure 4. Mean approach tendencies (RT push – pull) for alcohol and softdrink cues. There was a significant interaction effect of drink type × group (p<.01), with alcohol cues being approached faster in alcohol-dependent patients as a trend (p<.06). Error bars depict 1 standard error (SE) above and below the mean.

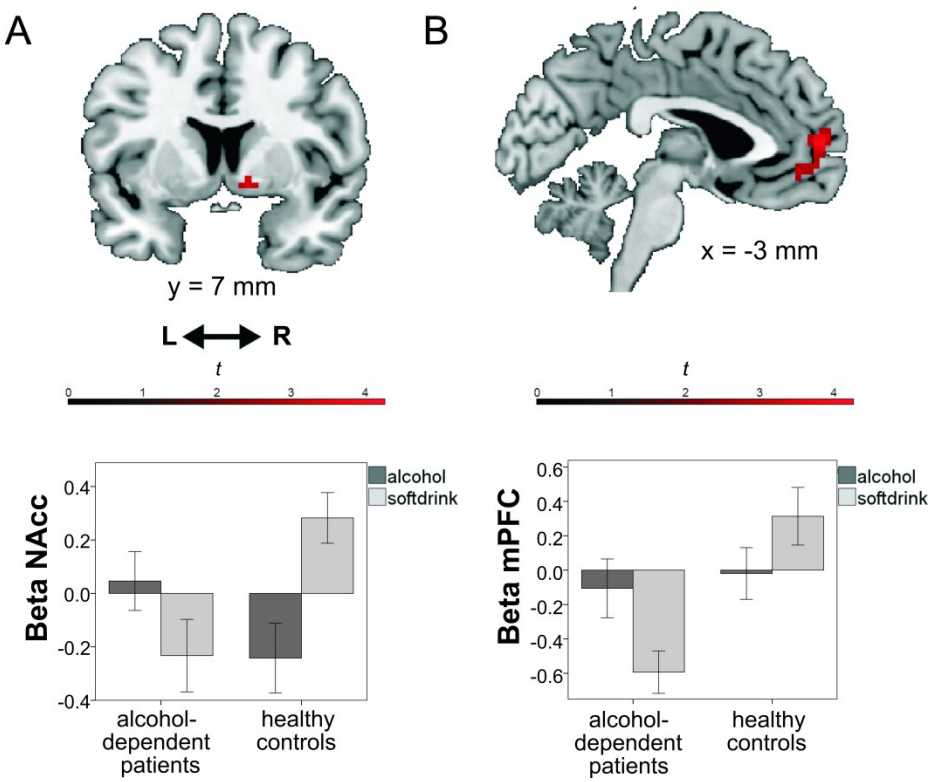

Figure 5. NAcc (panel A) and mPFC (panel B) showed higher BOLD response in alcohol-dependent patients compared to healthy controls in the alcohol approach bias contrast (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink). The effects were significant at $p<.05$ (FWE, SVC). For visualization, activations within our NAcc ROI and our mPFC ROI are plotted on a standard anatomical brain template with a threshold of $p<.005$ uncorrected.

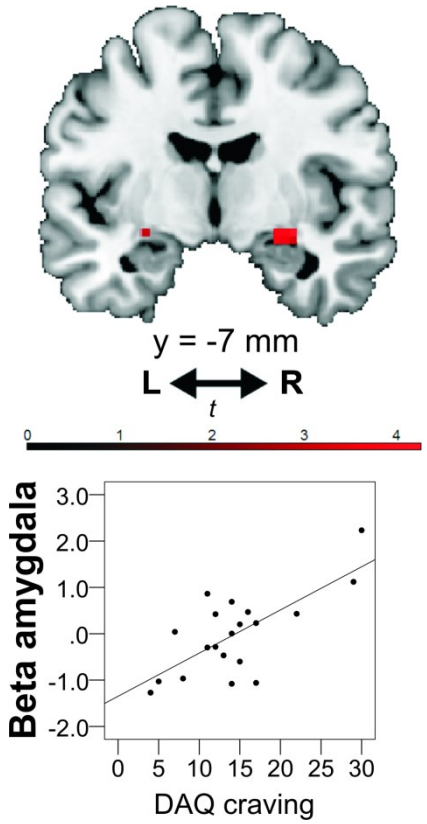

Figure 6. DAQ alcohol craving scores correlated positively with alcohol approach bias-related brain activity in the amygdala in alcohol-dependent patients (p<.05, FWE, SVC). Activations within the amygdala ROI are plotted here on a standard anatomical brain, with a threshold of p<.005 uncorrected.

4.3 Experiment III: Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol-dependence

As summarized in the introduction, the presentation of alcohol cues to alcohol-dependent patients evokes relatively strong activation in mesolimbic brain areas, such as the NAcc and amygdala (Heinz et al., 2009; Schacht et al., 2013). The strength of this neural cue reactivity has been associated with craving (Myrick et al., 2004) and alcohol consumption after relapse (Beck et al., 2010; Beck et al., 2012; Grusser et al., 2004). Moreover, as shown in the previous experiment, automatic alcohol approach bias-related amygdala activation correlated positively with alcohol craving in alcohol dependent patients (C. E. Wiers et al., 2014). CBM training has the goal to selectively retrain approach biases and has been shown to reduce relapse rates one year after training (Eberl et al., 2013; R. W. Wiers et al., 2011). Whether CBM can influence neural alcohol cue reactivity in patients as yet remains unknown.

We therefore performed a double-blind placebo-controlled randomized study, in which thirty-two abstinent alcohol-dependent patients were assigned to a CBM group (n=15) or a placebo training group (n=17). Both groups performed an approach avoidance joystick task (AAT) for 3 weeks in the Salus Clinic Lindow. The CBM group pushed away 90% of alcohol cues on the AAT with a joystick, whereas this rate was 50% in the placebo group (see paragraph 3.1.2 for details on the training). Before and after training, alcohol cue reactivity (i.e., passive viewing of alcohol versus softdrink cues) was measured with fMRI.

Before training, patients pooled over both groups demonstrated significant cue-evoked activation in the bilateral amygdala, and at trend level in the left NAcc (Figure 7). Activity in both areas correlated positively with subjective alcohol craving scores before training, which replicates previous alcohol cue reactivity studies (e.g., Grusser et al., 2004; Heinz et al., 2009; Koob & Volkow, 2010; Schacht et al., 2013).

Although expected, there was no significant interaction effect of group × time on alcohol approach bias scores. However, exploratory paired t- tests showed an effect in the hypothesized direction: a decrease of the alcohol approach bias in the CBM group by trend, but not in the placebo group. After training, the CBM group showed greater reductions in cue-evoked activation in the bilateral amygdala, compared to the placebo group (Figure 8). Decreases in craving scores were correlated with decreases in amygdala activity within the CBM group but not in the placebo group (Figure 9). There were no effects of training found in NAcc activations.

These findings provide the first evidence that CBM affects cue-induced mesolimbic brain activity. Reduction of neural cue reactivity may be the underlying mechanism of the therapeutic effectiveness of CBM, potentially by reducing the salience of alcohol cues as proposed by (R. W. Wiers et al., 2013). In the next chapter the findings of the three experiments are discussed in light of incentive sensitisation and dual process models of addiction.

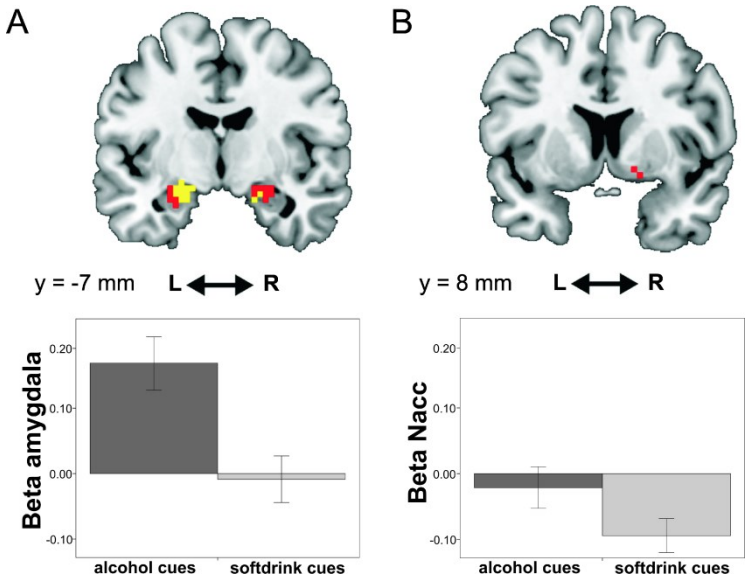

Figure 7. Before training, both groups of alcohol-dependent patients showed significant alcohol cue reactivity (alcohol-softdrink) in the bilateral amygdala (p<.05 FWE SVC; panel A), and in the right nucleus accumbens as a trend (p=.057 FWE SVC; panel B). Error bars depict 1 SE of the mean. For graphical purposes, significance levels of p=.05 (red) and p=.005 (yellow) uncorrected were used to plot activations.

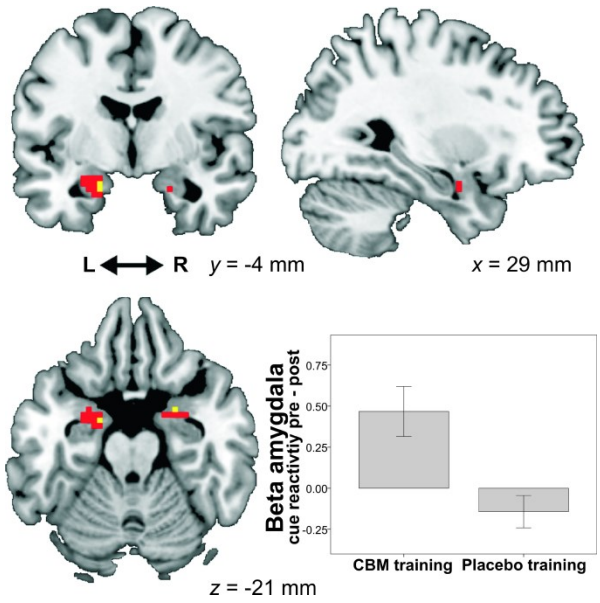

Figure 8. Change of pre-post cue reactivity in the CBM group versus the placebo training group. While activation in the bilateral amygdala was reduced in the CBM trainings group (p<.05 FWE SVC), there was no reduction in the placebo trainings group, not even at p<.005 uncorrected. Error bars depict 1 SE of the mean. For graphical purposes, significance levels of p=.05 (red) and p=.005 (yellow) uncorrected were used to plot activations.

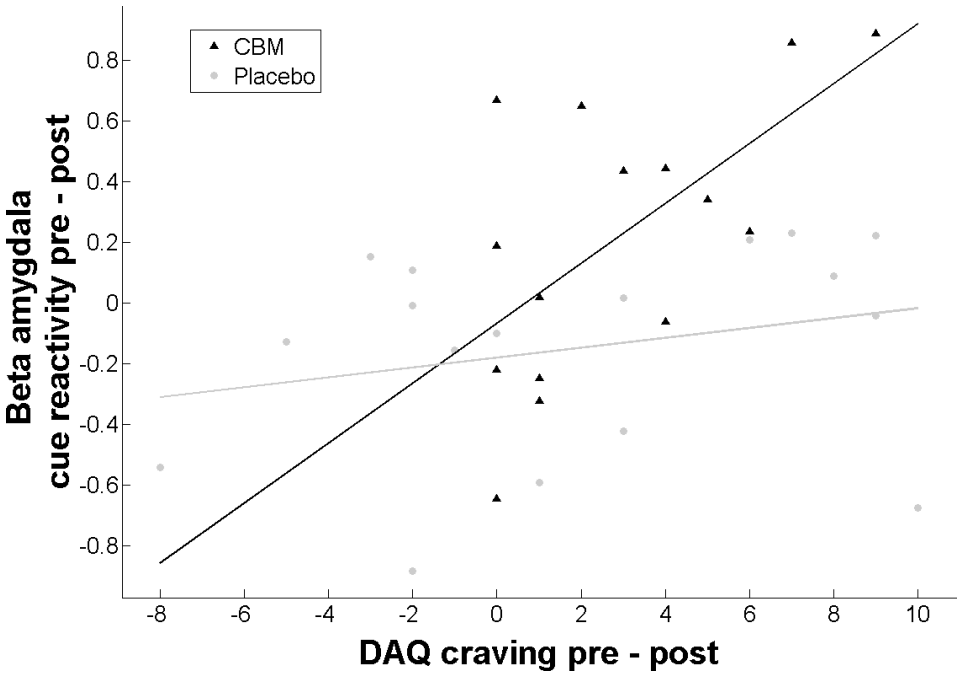

Figure 9. Correlation of the pre-post training change in amygdala cue reactivity (alcohol-softdrink) with DAQ scores in the CBM and placebo training group. In the CBM group (black triangles), the difference of pre-post amygdala activations correlated significantly with the decrease in DAQ alcohol craving, whereas this was not the case for the placebo training group (gray dots). Beta values of activations within the amygdala ROI were extracted per subject at p=.005 uncorrected.

CHAPTER 5
DISCUSSION AND FUTURE DIRECTIONS

In this chapter I first discuss how the three empirical studies summarized in the previous chapter, provide answers to the research questions formulated in chapter 2. The findings are discussed in light of the incentive sensitisation model and dual process models of addiction. Second, I propose a model that combines elements of existing psychobiological models on biased motivation in addiction and the key findings of this thesis. Finally, I discuss the limitations of the studies and explore future research possibilities.

5.1 Discussion of research questions

First question: Do drug users have an automatic approach bias for drug cues on the AAT? Is the strength of this bias related to drug craving?

Experiment I and II

In the first two experiments we found that heavy smokers and alcohol-dependent patients had stronger approach tendencies for drug cues compared to non-addicted control groups. In smokers, but not in alcohol-dependent patients, these tendencies correlated positively with craving scores.

Approach tendencies assessed with the AAT have been previously described in alcohol-dependent patients (Ernst et al., 2012; R. W. Wiers et al., 2011), heroin abusers (Zhou et al., 2012) and in cannabis users (Cousijn et al., 2011). Our findings add to the literature in that we replicate the phenomenon in alcohol addiction and are the first to show this behaviour in tobacco-dependent individuals. These findings therefore suggest a common underlying pathway of approach tendencies in drug addiction, independent of drug-specific mechanisms. The automatic drug approach bias could serve as a marker for addictive states and could help develop new forms of treatment for drug addiction.

The association of automatic approach tendencies with explicit craving, as shown in smokers, is in accordance with the incentive sensitisation theory of addiction, suggesting that incentive sensitisation (involving, amongst other things, automatic approach reactions) and craving are

related. However, we neither found this correlation in alcohol-dependent patients, nor has it been reported in previous approach bias literature on the AAT in addicted in alcohol-dependent patients (R. W. Wiers et al., 2011), heroin abusers (Zhou et al., 2012) or heavy cannabis users (Cousijn et al., 2011). A possible explanation for this is that in smokers, the time in between drug-taking is generally shorter compared to other drug-users. This may lead to higher levels of craving after a short period of time. Moreover, the alcohol- and heroin- dependent individuals in previous studies were in treatment programs and already abstinent from the drug for several months, which may have influenced explicit craving ratings.

Second question: Do former drug users still show an automatic approach bias to drug cues after long-term abstinence?

Experiment I

The results of our first experiment confirmed our hypothesis: ex-smokers were expected to reveal a diminished approach bias for smoking cues compared to smokers, which was, indeed, shown. That is, ex-smokers' approach tendencies for smoking cues were significantly smaller than tendencies of current-smokers. In fact, ex-smokers' approach tendencies for smoking cues did not differ from tendencies of never-smokers. Although the experiment was the first to study the automatic drug approach bias in ex-smokers, the results are in line with a previous study on attentional bias (Munafo et al., 2003), that likewise revealed no difference in smoking cue vigilance between ex-smokers and never-smokers on a visual probe task. Still, other studies did not find a diminished attentional bias in ex-smokers compared to heavy smokers on the smoking Stroop task (Munafo & Johnstone, 2008; Munafo et al., 2005) and on a visual attentional bias task (Nestor et al., 2011). Nevertheless, the results suggest that if mesolimbic neuroadaptations do indeed underlie the approach bias in current smokers, these neuroadaptations are not permanent but can either be reversed or inhibited after cessation. In this way, our findings do not confirm Robinson and Berridge's prediction that neuroadaptations and sensitisation are stable over abstinence, at least for smoking. Furthermore, the incentive sensitisation theory also predicts craving and sensitisation to be related (Robinson and Berridge 1993). In our study, none of the ex-smokers reported craving. It could therefore be that automatic biases decrease over abstinence, as a result of decreased craving or decreased rewarding effects of drugs. Alternatively, ex-smokers may have found strategies to control their approach behaviour to smoking cues, as

suggested by dual process models of addiction (e.g., R.W. Wiers et al., 2007). The present AAT study, however, could not distinguish between these two possible explanations (i.e., diminished motivation or increased control over this motivation) of the results. In sum, the results suggest that incentive salience and automatic approach tendencies for drug cues are not strictly permanent in life and diminish over long-term abstinence.

Third question: What are the neural correlates underlying the drug approach bias in drug-addicted individuals? Are these correlates related to subjective drug craving?
Experiment II

The results of our second experiment suggested that an overactive motivational brain system, rather than a suboptimal cognitive control system, underlie the automatic drug approach bias in drug addiction. Namely, we showed that motivational brain areas were involved in the alcohol approach bias: first, the NAcc and mPFC were more active in alcohol-dependent patients compared to healthy control participants during the approach of alcohol as compared to softdrinks. These are areas that have previously been shown to play a role in alcohol cue reactivity, reward processing and the motivational value of stimuli (Braus et al., 2001; Grusser et al., 2004; Hare et al., 2009; Heekeren et al., 2007; Heinz et al., 2009; Kahnt et al., 2010; Park et al., 2011). Second, alcohol approach bias-related brain activity in the amygdala correlated positively with alcohol craving scores in patients. The amygdala is an area known to play a key role in motivational salience and the consolidation of emotional memories (Cunningham & Brosch, 2012; Cunningham et al., 2008; Koob & Volkow, 2010; Mahler & Berridge, 2009). This finding is in line with previous neuroimaging findings that also showed a positive relation between activity in the amygdala while passively viewing alcohol cues and subjective craving (Childress et al., 1999; Koob & Volkow, 2010). Drug craving may thus be associated with increased emotional memories of the abused drug while approaching it. Since the NAcc and mPFC were not related to subjective craving in patients, these areas may mainly be involved in automatic approach reactions rather than explicit subjective judgments of drug craving, whereas the amygdala is only activated in patients that are explicitly aware of their craving.

However, we did not find direct support for either enhanced or decreased neural inhibitory control (i.e., we found no differences in dlPFC activations) while patients were avoiding alcohol.

Since alcohol-dependent patients were all clinic inpatients, it may be that avoiding alcohol cues was not completely incongruent for this population because of experience- or intervention-based avoidance associations interfering with drug-related incentive salience. This could explain why the dlPFC was not consistently activated for avoiding alcohol. Future studies could investigate whether neural correlates of the alcohol approach bias in social or hazardous drinkers for whom drinking is not (yet) problematic would involve dlPFC activity for avoiding alcohol.

These findings hence support incentive sensitisation models of addiction that propose mesocorticolimbic neuroadaptations to underlie the automatic approach bias to drug cues in addicted individuals (Robinson & Berridge, 1993, 2003). However, the findings do not find evidence for a suboptimal control system, as proposed by dual process models of addiction (Bechara, 2005; R. W. Wiers et al., 2007)

Fourth question: What are the effects of CBM on neural drug cue reactivity in drug-dependence? Are these neural effects related to effects of CBM on drug craving?
Experiment III

The results of our third experiment suggest that CBM can affect drug cue-induced mesolimbic brain activity in drug-dependence. We found that CBM training led to reductions in bilateral amygdala activations in the CBM compared to the placebo group, which covaried with reductions in subjective drug craving score. Therefore, reduction of alcohol cue-induced amygdala activity may be a key underlying mechanism of the therapeutic effectiveness of CBM.

The amygdala has been associated with craving while passively viewing drug cues (Childress et al., 1999; Koob & Volkow, 2010), while approaching versus avoiding alcohol cues on the AAT in our second experiment (C. E. Wiers et al., 2014) and with motivational salience of stimuli (Cunningham & Brosch, 2012; Cunningham et al., 2008). Moreover, it has been shown that the amygdala can be flexibly modulated over time in alcohol cue reactivity by a combination of pharmacological and behavioural therapy (Schneider et al., 2001). Therefore, a possible interpretation of the current results is that CBM reduces the motivational salience of alcohol cues.

The question then arises how CBM could cause such a reduction in salience. It may be that this effect is globally related to recent findings on inhibition training (Houben, Nederkoorn, Wiers, & Jansen, 2011; Veling & Aarts, 2009; Veling, Holland, & van Knippenberg, 2008), showing 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 CBM (i.e., actively and habitually avoid previous desired alcohol cues) causes a similar effect: patients could solve the avoid-alcohol problem by reducing the overall salience of alcohol cues (R. W. Wiers et al., 2013) and hence reduce behavioural biases associated with them. Future studies are needed to provide evidence for or against this possibility that the mediating mechanism of CBM involves, at least partially, reductions in salience.

In conclusion, these results suggest that CBM can reduce the motivational salience of drug cues encoded in the amygdala. This finding can help to better understand the underlying mechanisms of the clinical effects of CBM which may lead to improved CBM methods. Further, fMRI measurements may prove useful in predicting whether CBM will be effective for individual patients.

5.2 Relating current findings to a psychobiological model of the drug approach bias

The experimental findings of this thesis lead to an improved understanding of the underlying neural processes of the automatic drug approach bias, its adaptability over abstinence and the neural effects of CBM. In this paragraph, I propose a psychobiological model which combines elements from previous models in addiction and my own findings (Figure 10).

Figure 10 shows a schematic overview of processes and components important to addiction, as proposed by the incentive sensitisation theory (Robinson & Berridge, 2003) and interpreted by Stephens (2008), dual process models (R. W. Wiers et al., 2007), research on automatic processes in addiction (Field & Cox, 2008) and the findings of this thesis. As explained in the introduction, through drug-associative learning processes drug-addicted individuals develop incentive salience regarding conditioned drug cues due to mesolimbic neuroadaptations, especially in the NAcc, mPFC and amygdala. These motivational processes lead to drug craving and approach tendencies to drug cues and are inhibited by a cognitive control system (especially the dlPFC). Drug craving and automatic biases are hypothesized to be mutually excitatory (Field & Cox, 2008).

On the basis of our experiments we provide new insights regarding the components of this model, indicated by the numbers 1 to 4 in Figure 10:

1. Craving is related to the strength of the drug approach bias. This relation may, however, be dependent on the drug of abuse or addicted population, because of differences in social desirability in craving reports, wishes to remain abstinent of the drug or the frequency of drug use.

2. Based on our findings in smokers and ex-smokers, long-term drug abstinence appears to decrease the automatic drug approach bias and subjective drug craving. Abstinence may also directly decrease incentive salience, as has been suggested by Nestor et al. (2011). Alternatively, cognitive control over salience, craving and drug approach bias may increase. To inform salience after abstinence, future neuroimaging studies on motivational and control brain areas in former drug users are needed.

3. Mesocorticolimbic brain areas (especially the NAcc, mPFC and amygdala) are related to the automatic drug approach bias. The NAcc and mPFC may be mainly involved in automatic approach reactions, whereas the amygdala may be related to explicit judgements of drug craving.

4. Effects of CBM on addictive behaviours involve decreasing the salience of drug cues encoded in the amygdala. Decreases in amygdala activations covary with changes in subjective craving. Whether reductions in salience are mediated by the drug approach bias should be further explored in future research.

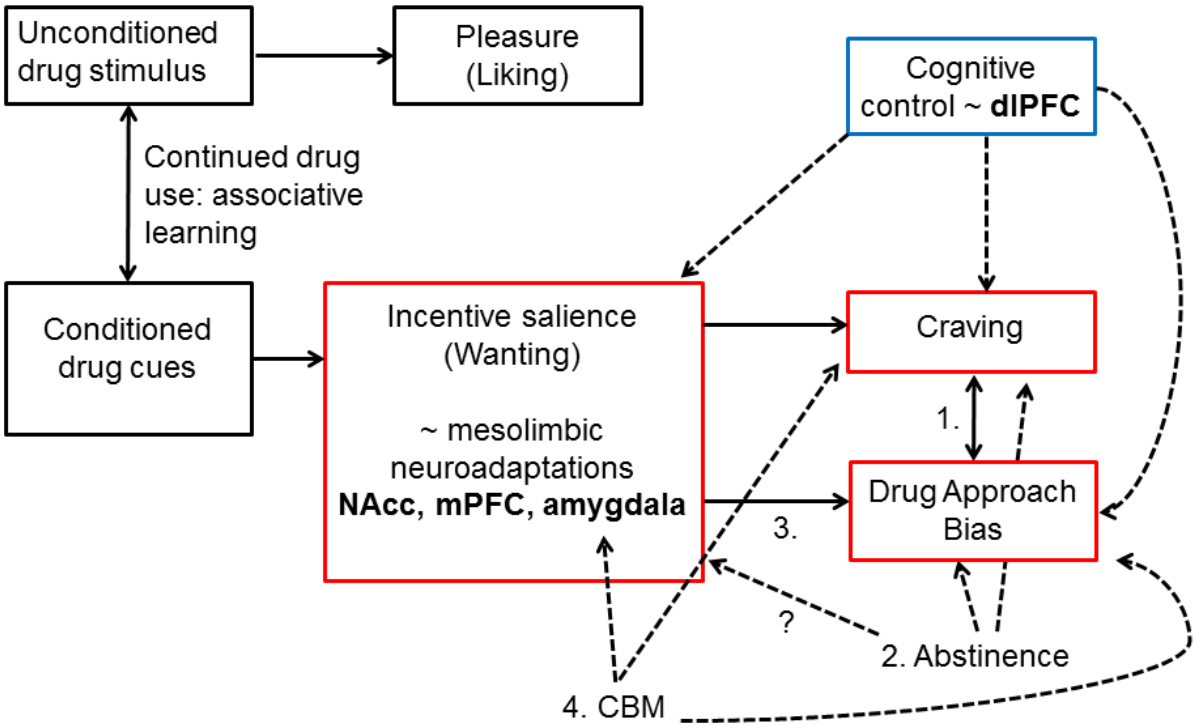

Figure 10. Schematic overview of processes relevant for drug addiction. This model is derived from the incentive sensitisation theory (Robinson & Berridge, 1993, 2003) as interpreted by Stephens (2008), dual process models of addiction (Bechara, 2005; R. W. Wiers et al., 2007) and research findings of this thesis. The incentive sensitisation theory and dual process models suggest that through repetitive associative learning, drug cues increase in incentive salience due to mesolimbic neuroadaptations. This leads to subjective drug craving and drug approach tendencies. It is hypothesized that craving and automatic biases are mutually excitatory (Field & Cox, 2008). According to dual process models, a cognitive control system is hypothesized to inhibit motivational processes (incentive salience, craving and the drug approach bias). The results of the current thesis provide new insight into the components of this model by suggesting that 1. The drug approach bias and craving are related (at least in heavy smokers); 2. Long-term drug abstinence decreases the automatic drug approach bias and subjective drug craving (possibly due to a reduction in salience of drug cues); 3. Mesolimbic brain areas are related to the automatic approach bias; 4. CBM decreases the salience of drug cues and inhibits the drug approach bias, resulting in reductions in craving.

5.3 Limitations and future directions

Some limitations of the three studies have to be considered.

First, in this thesis, the behavioural drug approach bias was defined as the interaction of picture category (drug vs. neutral) × movement (approach vs. avoid). The (avoid – approach) subscores per picture category were termed approach tendencies for drugs or approach tendencies for neutral cues. However, there has been little consensus about this terminology in the approach bias literature: most previous publications defined the behavioural subscores of (RT avoid – approach drug cues) and (RT avoid – approach neutral cues) the approach bias for drug and neutral cues respectively (Cousijn et al., 2011; Ernst et al., 2012; R. W. Wiers et al., 2011; R. W. Wiers et al., 2010) and in the original publication of our first study (C. E. Wiers et al., 2013). Other labs named these subscores "behavioural preference score" (e.g., Ernst et al., 2012; Ernst et al., 2011), or defined the subscores as approach score = RT (approach neutral – approach drug) and avoid score = RT (avoid neutral – avoid drug) (e.g., Zhou et al., 2012). Importantly, all drug approach bias publications had the behavioural interaction effect of picture type (drug vs. neutral) × movement (approach vs. avoid) as their main analysis, which is why this score is used in the current thesis. Future studies should use consistent terminologies in order to know what is exactly meant with the drug approach bias.

Second, conflicting results appeared in behavioural and neural approach tendency scores in our second experiment. As hypothesized, post-hoc tests on behavioural approach tendency scores were stronger in drug-dependent individuals compared to non-addicted control groups (C. E. Wiers et al., 2013; C. E. Wiers et al., 2014). In contrast, group differences in neural responses in the NAcc and mPFC were mainly due to differences in responses to softdrinks rather than to alcohol cues (C. E. Wiers et al., 2014). Moreover, the decrease in amygdala activation after CBM training in experiment III (C. E. Wiers et al., under review), was due to decreased amygdala activation for alcohol cues, but also to upregulated activation for softdrink cues (however not further explored and not plotted in Figure 7). Although the inclusion of a neutral category is important in such analyses to correct for general BOLD activations, these effects may well be meaningful. It may be that the alcohol approach bias is due to decreased motivational brain responses to naturally rewarding stimuli, such as softdrinks, rather than an increased motivational response to alcohol. This is in line with previous studies showing that addicted individuals

demonstrate reduced reward-related activation to naturally rewarding stimuli compared to controls (e.g., Volkow et al., 2004; Wrase et al., 2007). Future fMRI studies should assess in detail whether increased alcohol cue-evoked reactivity is indeed due to enhanced reactivity to alcohol cues, or rather (or additionally) due to reduced reactivity to natural rewards. This could have implications for treatment: rather than attempting to reduce the appeal of alcohol, one could promote the appeal of naturally rewarding stimuli. The approach of natural rewarding softdrinks in 90% during AAT-based CBM training schemes may be an important contributing factor for the clinical effectiveness of CBM and may be beneficial over drug cue exposure treatments that "only" target drug-based cue reactivity (e.g., Vollstadt-Klein et al., 2011). This possibility should be further explored in future research.

Third, the duration of abstinence of patients varied between 1 week and 6 months in the second experiment (C. E. Wiers et al., 2014) and 1-4 months in our third experiment (C. E. Wiers et al., under review). This may have influenced craving and automatic processes. However, length of abstinence was neither negatively correlated with BOLD responses in our ROIs in the approach alcohol contrast, nor with BOLD responses in the dlPFC in the avoid alcohol contrast. Moreover, abstinence was not related to cue reactivity in experiment III. Therefore, mesocorticolimbic brain responses may be independent of these relatively short periods of abstinence and could hence play a significant role in relapse.

Fourth, our studies could not provide information on relapse, as it did not include a follow-up.
It would be interesting to follow up drug-dependent individuals and determine whether approach bias scores, related neural activity or changes in mesolimbic cue reactivity predict outcome. Moreover, a longitudinal approach on drug approach tendencies after cessation could be an interesting design. It may be that the drug approach bias is predictive for relapse.

Fifth, the third experiment considered cue reactivity rather than neural activity related to approach/avoidance tendencies for alcohol (C. E. Wiers et al., under review). In our second study the NAcc and amygdala were found to be related to the alcohol approach bias in alcohol-dependent patients (C. E. Wiers et al., 2014). Although C. E. Wiers et al. (under review) found intervention effects on cue reactivity in similar areas, CBM effects on approach/avoidance conflicts may involve different processes that would not be found in cue reactivity designs.

Future studies are needed that focus on effects of CBM in an approach avoidance context, rather than passive viewing, as it can better disentangle the roles of the proposed motivational and cognitive control system by dual process models of addiction.

5.4. Conclusion

In conclusion, the results of this thesis suggest that various drug-addicted populations have automatic tendencies to approach drug cues. Drug approach tendencies may therefore not be drug-specific but rather are the result of a general mechanism in addiction. The drug approach bias may diminish over long-term abstinence and hence, incentive salience to drug cues may not strictly be permanent in life. A more overactive motivational brain system, rather than a less active cognitive control system is associated with the drug approach bias in addiction. Even when addicted individuals express an explicit wish to remain abstinent, reflexive embodied reactions to drug cues and motivational brain mechanisms are likely to make individuals vulnerable for relapse. CBM training in which addicted individuals actively learn to avoid drug cues, decrease drug cue-evoked amygdala activation. A decrease of salience, as encoded in the amygdala, may thus be a key mechanism of the therapeutic effectiveness of CBM.

The findings have implications for the treatment of drug addiction. Treatment generally focuses on the improvement of conscious control (e.g., cognitive behavioural therapy or counselling) and reduction of craving by pharmacotherapy. However, our current results and recent clinical effects of CBM (Eberl et al., 2013; R. W. Wiers et al., 2011) suggest the automatic drug approach bias as a potential target for clinical intervention. CBM has the advantage that the intervention is fast, safe and cheap. A recent article in the Economist (2011) described training as a promising new treatment for addiction, which "may put the psychiatry couch out of business". Although the treatment is indeed promising, further research is necessary to further explore the working mechanisms and clinical efficacy of CBM as an intervention in clinical practice.

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SUPPLEMENTS

A Research articles

Experiment I

Wiers CE, Kühn S, Javadi AH, Korucuoglu O, Wiers RW, Walter H, Gallinat J, Bermpohl F (2013). Automatic approach bias towards smoking cues is present in smokers but not in ex-smokers. *Psychopharmacology, 229*(1): 187-197. doi: 10.1007/s00213-013-3098-5

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Experiment II

Wiers CE, Stelzel C, Park SQ, Gawron CK, Ludwig VU, Gutwinski S, Heinz A, Lindenmeyer J, Wiers RW, Walter H[*], Bermpohl F[*] (2014). Neural correlates of alcohol-approach bias in alcohol addiction: the spirit is willing but the flesh is weak for spirits. *Neuropsychopharmacology, 39*(3), 688-697. doi: 10.1038/npp.2013.252

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Experiment III

Wiers CE, Stelzel C, Gladwin TE, Park SQ, Pawelczack S, Gawron CK, Stuke H, Heinz A, Wiers RW, Rinck M, Lindenmeyer J, Walter H[*], Bermpohl F[*]. Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol-dependence.
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EXPERIMENT I – AUTOMATIC APPROACH BIAS TOWARDS SMOKING CUES IS PRESENT IN SMOKERS BUT NOT IN EX-SMOKERS

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Abstract

Rationale: Drug-addicted individuals show automatic approach tendencies towards drug-related cues, i.e., an approach bias (ApB). Nevertheless, little is known about ApB in tobacco smokers and about the presence of ApB after smoking abstinence.

Objectives: We investigated ApB to smoking cues in heavy tobacco smokers versus never-smokers and studied its relation to smoking characteristics and craving. Second, we compared ApBs of heavy smokers with biases of abstinent heavy smokers.

Method: A group of current heavy smokers (n = 24), ex-smokers who were abstinent for at least 5 years (n = 20), and never-smokers (n = 20) took part in the experiment. An indirect smoking approach avoidance task was performed, in which participants were required to respond to pictures of smoking and neutral cues by pulling (approach) or pushing (avoid) on a joystick, according to the content-irrelevant format of the picture (landscape or portrait). Craving scores were examined using the Questionnaire of Smoking Urges.

Results: Heavy smokers showed an ApB for smoking cues compared to ex-smokers and never-smokers, which correlated positively to craving scores. There were no group differences in ApB scores for ex-smokers and never-smokers.

Conclusion: These results suggest that ApBs for smoking cues are present in heavy smokers and decrease after long-term successful smoking cessation.

Introduction

A paradox in addictive behaviors is the continuation of drug use despite known long-term negative outcomes (Stacy and Wiers 2010). Most cigarette smokers strongly desire to quit, but few succeed, with 80 % of smokers relapsing within 1 year after their supposedly last cigarette (Hughes et al. 2008). Why some people are able to quit smoking successfully, whereas others are not and relapse, remains poorly understood. One important factor for relapse may be the degree to which smoking cues trigger a motivational reaction to smoke again, which happens largely outside conscious awareness (Ferguson and Shiffman 2009). This reaction is hypothesized to develop during the transition from voluntary to compulsive usage, due either to sensitization to drug cues (Robinson and Berridge 1993, 2003), habitual stimulus–response learning (Robbins and Everitt 1999; Tiffany 1990), or both (Mogg et al. 2005). Additionally, addiction has been described as a disorder of disrupted self-control over automatically triggered impulses to use (Baler and Volkow 2006). Together, as formulated by dual process models, both an overactive approach-oriented motivational system and a less sufficient regulatory control system may lead to compulsive continuation of a drug, without explicitly wanting this (Bechara 2005; Wiers et al. 2007).

Experimental evidence for motivational cue reactivity in addiction comes from research on automatic biases in several drug-dependent populations (see Stacy and Wiers 2010 for a review). In these studies, substance users show automatic selective attention to drug-related as compared to neutral cues (attentional bias) as well as the tendency to approach these cues faster rather than avoid them (approach bias, ApB), which is typically not seen in control groups. Attentional bias and ApB are measured by means of various computerized implicit reaction time (RT) tasks, in which participants' RT biases are assessed without explicitly asking participants. Such tasks are considered implicit or automatic if the instruction is indirect (i.e., participants are largely unaware of the task's outcome measures) or if the outcome measures meet at least one of a set of properties: being fast, goal-independent, or not directly controllable (De Houwer 2006; Stacy and Wiers 2010). Because of these criteria, implicit measures are less susceptible to social desirability than explicit measures and could measure automatic processes that lie outside of conscious awareness (De Houwer 2006). For example, Huijding and de Jong (2006) provided evidence that implicit measures better predict more automatic aspects of behavior, whereas explicit measures better estimate controlled behavior.

Over the last decade, a wealth of studies has focused on attentional biases in tobacco addiction. First, tobacco smokers have been shown to be slower in responding to smoking-related words compared to neutral words in a smoking Stroop task (Drobes et al. 2006; Munafo et al. 2003, 2005; Waters et al. 2003b), suggesting distraction by smoking cues. Moreover in pictorial visual cue tasks, smokers have shown to fixate longer on smoking cues compared to neutral cues (Bradley et al. 2008; Chanon et al. 2010; Mogg et al. 2003; Munafo et al. 2005; Waters et al. 2003a). However, only a few studies have concentrated on automatic action tendencies elicited by tobacco cues by studying the ApB. So far, five studies using the Stimulus–Response Compatibility (SRC) task have been reported, in which participants move a manikin towards (approach) and away from cues (avoidance) on a computer screen. At the start of each trial, the manikin is positioned either above or below the target stimulus. Approach/avoidance movements are to be made by moving the manikin downward or upward (or vice versa if the stimulus is below the target) with button presses (arrow pointing up/down). Smokers have been shown to

move the manikin faster towards smoking cues than towards neutral cues and, hence, reveal a smoking ApB (Bradley et al. 2004, 2008; Mogg et al. 2003, 2005; Thewissen et al. 2007).

The incentive sensitization theory of addiction suggests a common underlying mechanism of attentional bias and ApB. All drugs release dopamine in the mesocorticolimbic system, a response that becomes sensitized after repeated drug use. Because of Pavlovian drug cue–reward associations, drug cues acquire incentive sensitization and consequently both grab the drug user's attention and elicit approach behavior (Robinson and Berridge 1993, 2003). Indeed, the strength of smoking attentional bias and ApB in smokers was positively correlated in two studies (Mogg et al. 2003, 2005), whereas this relation was not pursued in a third study measuring both automatic biases in a smoking and a never-smoking control group (Bradley et al. 2008). Despite the common mechanism of the phenomena, there are also differences. Probably the most important difference between the two biases is that, although the mechanism of attentional biases for cigarettes most likely lies in attentional capture (Chanon et al. 2010), the ApB is unique in that it embodies direct motor movements towards drug cues. While motor movements have to be compatible with individuals' own interpretation of actual approaching and avoiding (Watson et al. 2012), they are of particular interest as they might represent incentive sensitization to a drug. In animal models, sensitization is operationalized as locomotor activity in reaction to drugs or drug cues over the course of recurrent but intermittent drug supply (Mead and Stephens 1998), whereas in humans, such an operationalization has not yet been described. Given that smoking is a highly rewarding motor skill and smokers recently showed activation in action-related brain areas while watching smoking cues (Wagner et al. 2011), it is surprising that only little research on automatic action tendencies for smoking cues in cigarette smokers has been conducted.

In this study, smoking ApBs were studied with a recently developed approach avoidance task (AAT). Originally, in studying biases for fearful stimuli (Rinck and Becker 2007), the AAT has been successfully implemented to measure automatic approach avoidance action tendencies in addiction. The AAT has at least two benefits over the SRC. First, the participants' movements are accompanied with a visual zooming function: the pictures increase and decrease in size upon an approach movement (pulling a joystick) or an avoidance movement (pushing a joystick), respectively. In this way, the combination of pull/push movements with visual feedback during AAT better resembles the approach and avoid tendencies towards and away from oneself than the upward and downward movements on the SRC (Krieglmeyer and Deutsch 2010). Second, whereas in the SRC participants are explicitly instructed to move the manikin towards or away from drug-related or drug-unrelated stimuli in separate blocks, the AAT makes use of irrelevant feature instruction. Participants are asked to respond to a feature that is irrelevant to the task, namely the format instead of content of the stimuli. ApB is calculated by the RT difference between pushing and pulling cues (drug related or neutral). In this way, the AAT is relatively implicit in both outcome measure as well as instruction, which makes it less likely that participants are aware of the task and, hence, more likely to measure more automatic processes (De Houwer 2003). So far, ApBs measured with the AAT have been shown in heavy drinkers (Wiers et al. 2009), alcohol-dependent patients (Ernst et al. 2012; Wiers et al. 2011), heroin abusers (Zhou et al. 2012; though this study used a relevant feature instruction), and in cannabis users (Cousijn et al. 2011), whereby drug users pull faster than push cues of the abused drug compared to a nonaddicted control group. As yet, it remains unknown whether smokers reveal smoking ApBs on the AAT against a control group, which was the first goal of the present study.

Both the attentional and approach bias have been associated with motivational measures of drug use and clinical measures. For example, there is an accumulation of evidence that smokers' attentional bias and ApB for cigarettes correlate positively with craving scores (Mogg et al. 2003, 2005; Waters et al. 2003a; Watson et al. 2013) and predict relapse (Janes et al. 2010; Waters et al. 2003b) as well as smoking behavior (Waters and Feyerabend 2000). Moreover, manipulating automatic biases by bias modification training programs can, in turn, influence drug motivations and relapse. For example, Attwood et al. (2008) showed that increasing attentional biases in cigarette smokers led to more craving for tobacco, and modification of ApB for alcohol in alcohol-dependent patients resulted in decreased rates of relapse against placebo-training groups (Eberl et al. 2013; Wiers et al. 2011). These studies show that automatic biases may play a causal role in craving, drug taking, and relapse. Researching automatic tendencies is, thus, particularly valuable as they form a potential target for the treatment of smoking addiction.

Whether the causation also goes the other way around, if automatic biases are decreased when drug taking is ceased, remains an open question. There is evidence that immediate smoking abstinence increases reinforcing properties of smoking and attentional bias for smoking words (Waters and Feyerabend 2000), whereas after 2 weeks of cessation, smoking reinforcement (Lussier et al. 2005), craving, and withdrawal symptoms (Yoon et al. 2009) decline. Whether automatic biases likewise reduce after long-term drug abstinence is largely unknown. According to the incentive salience model of Robinson and Berridge (1993, 2003), sensitization to drugs is (semi-)permanent, which could imply that they serve a causal role in relapse. Dual process models of addiction also suggest that drug-seeking tendencies remain but emphasize that successfully refraining from a drug requires the ability and willingness to control these tendencies (Wiers et al. 2007). Various studies on smoking cessation techniques have used attentional bias (but not ApB) as an outcome measure, with conflicting results. On the one hand, smokers have been shown to be able to decrease motivational cue reactivity by cognitive strategies such as cognitive reappraisal (Littel and Franken 2011) and bias modification training (Attwood et al. 2008). Conversely, Pavlovian extinction training in which drug cues are presented to smokers but remain unreinforced have been shown to decrease craving but not attentional bias in smokers (Kamboj et al. 2012). Overall, these studies provide first evidence that it is possible to decrease automatic biases, although the mechanisms behind this are poorly understood and direct evidence for ApB is lacking.

Moreover, it is unknown whether smokers who have been abstinent for years still reveal automatic biases. Studies measuring automatic biases in former smokers are scarce and provide contradictory results. Munafo et al. (2003) found that ex-smokers, who had been abstinent for over 4 years, have diminished attentional bias for smoking cues, suggesting that biases can fade away. Nonetheless, other studies with a similar design did not find direct RT differences between ex-smokers and smokers (Munafo and Johnstone 2008; Munafo et al. 2005; Nestor et al. 2011). Interestingly, Nestor et al. found that smokers have increased mesolimbic brain activity while watching smoking cues compared to ex-smokers, whereas prefrontal areas were more active in ex-smokers. Since these brain areas are involved in reward and cognitive control, respectively, this suggests that cue reactivity decreases after cessation, parallel to increased cognitive control. To date, no studies have investigated approach tendencies after long-term smoking cessation, which was the second goal of this study.

Therefore, the aims of the present study were twofold: first, we examined whether heavy smokers would have an ApB for smoking cues, compared to a never-smoking control group and whether

these scores related to self-reported craving. We expected smoking ApB to be larger in smokers than in controls and positively related to craving. Then, since the question remains whether ex-smokers who deliberately quit their heavy smoking still reveal an approach bias for cigarette cues, it was our second aim to compare ApBs in ex-smokers with never-smokers and heavy smokers. Although the literature on implicit or relatively automatic biases in ex-smokers provides conflicting results, we expected ApBs of ex-smokers to be smaller than of smokers and to be reduced after longer abstinence.

To diminish influencing variables other than abstinence between ex-smokers and smokers, the two groups were screened on smoking characteristics (duration of smoking >5 years, amount of cigarettes per day >15 cigarettes per day). We also assessed smoking attitudes (in ex-smokers in retrograde perspective, attitudes on when they were still smoking) to study potential motivational differences of such attitudes in smokers and ex-smokers. To inform the mechanism of ApB, we correlated ApB scores with smoking characteristics in smokers and ex-smokers. Previous studies showed a positive relation of attentional biases and smoking consumption (Waters and Feyerabend 2000) and of approach bias with cannabis addiction severity (Cousijn et al. 2011). Based on this, we hypothesized that the strength of approach bias was positively related to smoking in heavy smokers and ex-smokers. Furthermore, since addiction has been associated with increased impulsive personality traits (Everitt et al. 2008; Verdejo-Garcia and Perez-Garcia 2007), we compared the three groups on the Barrett Impulsiveness Scale (BIS). Impulsiveness is proposed to be related to reward sensitivity and lack of response inhibition in addiction (Dawe et al. 2004), but little is known about the relation between drug action tendencies and self-reported impulsiveness. To investigate whether current impulsiveness and self-control were related to the strengths of ApB, BIS subscales were correlated with ApB in each group. For smokers, we hypothesized the smoking ApB to be related with the BIS total score. In ex-smokers, we had particular interest in correlating ApB with the more cognitive subscales of BIS: self-control impulsiveness, and cognitive instability impulsiveness. We expected that ex-smokers who scored lower on these scales—reflecting higher levels of self-control and cognitive stability—would show a lower smoking ApB.

Methods

Participants

Twenty-four current cigarette smokers (mean age ± SD = 35.54 ± 10.35 years, 11 women), 20 ex-smokers (mean age ± SD = 41.75 ± 7.38 years, ten women), and 20 never-smokers (mean age ± SD = 37.40 ± 10.04 years, nine women) were recruited via an online advertisement. Due to a programming failure, two ex-smokers were presented with 29 % of trials presented in the AAT but were nevertheless included into the study's analyses [1]. Groups were matched for age, gender, and years of education (all $p > 0.09$, ns; see Table 1). Smokers were required to have smoked at least 15 cigarettes per day for a period of at least 5 years. Ex-smokers were considered eligible if they used to smoke more than15 cigarettes per day in their smoking period, were abstinent for a minimum of 5 years, and had not undergone nicotine replacement or other therapy to quit smoking. The never-smoking group never smoked more than two cigarettes over their lifetime.

Table 1. Demographic and smoking characteristics of heavy smokers, ex-smokers, and never-smokers

	Heavy smokers, n = 24, 11 females (42 %)		**Ex-smokers, n = 20, 10 females (50 %)**		**Never-smokers, n = 20, 9 females (45 %)**			
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***		***p* value**
Demographics							$F(2,61)$	
Age (years)	35.54	10.35	41.75	7.38	37.40	10.04	2.44	0.096
Digit symbol score	211.58	31.67	208.90	35.38	220.90	28.59	0.79	0.461
Years of education	15.10	3.21	15.05	3.62	16.85	4.07	1.64	0.202
Alcohol use (AUDIT)	3.50	2.38	2.35	1.81	2.80	1.88	1.75	0.183
EHI	91.11[a]	19.79	86.60	23.17	77.81	26.49	2.01[b]	0.141
BDI	21.35[a]	12.19	21.20	14.81	19.75	12.94	0.09[b]	0.913
Smoking characteristics					t(42)			
Age start smoking (years)	16.04	2.05	15.20	1.70	–	–	1.46	0.152
Smoking duration (years)	18.98	9.13	14.40	6.88	–	–	1.85	0.072
Cigarettes per day	22.71	5.32	24.50	9.04	–	–	−0.82	0.419
Pack years	22.75	14.40	18.95	14.27	–	–	0.88	0.387
Abstinence (years)	–	–	11.23	5.82	–	–	–	–
FTND	5.08	1.18	4.00	1.41	–	–	2.78	0.008**
DBS pro smoking	18.63	6.34	17.15	10.94	–	–	0.53[c]	0.598
DBS con smoking	18.50	8.02	18.60	9.43	–	–	−0.04	0.970
Craving							t(20)	
QSU total score	24.81[d]	11.27	0.00[e]	0.00	–	–	10.09	0.000***
QSU strong desire to smoke	19.14[d]	7.78	0.00[e]	0.00	–	–	11.28	0.000***
QSU relief from negative effect	2.27[d]	2.25	0.00[e]	0.00	–	–	5.68	0.000***
BIS impulsiveness					F(2, 61)			
BIS attention	9.13	2.15	9.35	2.85	8.30	2.30	1.04	0.358
BIS motor	15.17	3.38	14.40	2.50	14.30	3.01	0.03	0.976
BIS self-control	13.13	2.44	13.05	3.17	12.15	3.07	0.74	0.483
BIS cognitive complexity	12.21	2.26	11.40	2.04	11.25	2.69	1.09	0.343
BIS perseverance	6.46	1.79	6.90	1.80	6.95	1.84	0.49	0.613
BIS cognitive instability	5.79	1.53	5.55	1.28	4.90	1.29	2.36	0.103
BIS total	60.54	9.16	60.75	8.66	57.37	10.84	0.78	0.463

SD: standard deviation; AUDIT: alcohol use disorder identification test; EHI: Edinburgh handedness inventory; BDI: Beck depression inventory; FTND: Fagerström test of nicotine dependence; DBS: decision balance scale; QSU: questionnaire of smoking urges; BIS: Barrett impulsiveness scale.
*$p < .05$; **$p < .01$; ***$p < .001$. [a] $n = 23$; [b] $F(2.60)$; [c] Since assumption of homogeneity of variance is violated, the degrees of freedom are 29; [d] $n = 21$; [e] $n = 17$;

Participants were required to have normal vision, speak German fluently, be right-handed as confirmed by the Edinburgh handedness inventory (Oldfield 1971), and have no history of drug abuse or psychiatric illnesses according to DSM-IV criteria, as screened with the M.I.N.I. plus an International Neuropsychiatric Interview, German translation (Sheehan et al. 1998). Alcohol use was examined with the Alcohol Use Disorder Identification Test (AUDIT), and AUDIT scores above 8 were excluded (Saunders et al. 1993). Pack years were calculated by packyears=(number of cigarettes/day×years of smoking)/20, with 20 being the size of a common pack of cigarettes. This measure integrates the duration of smoking with the number of cigarettes and leads to a standardized value for measuring smoking consumption over a period of time (e.g., Nestor et al. 2011). The study was approved by the Ethical Committee of the Charité, Universitätsmedizin Berlin.

Procedure

To increase craving, smokers were abstinent of tobacco smoking for at least 2 h prior to the experiment. After given informed consent, questionnaires were filled out on a computer, following AAT performance. After completing the task, participants were paid, debriefed, and thanked for their time and assistance.

Questionnaires

Tobacco dependence was assessed by means of the Fagerström test of nicotine dependence (FTND; Heatherton et al. 1991). Smokers filled out the questionnaire about their current use (mean score ± SD = 5.08 ± 1.18) and ex-smokers filled out the FTND with retrograde perspectives of their smoking period (mean score ± SD = 4.00 ± 1.41). Before the task, smokers and ex-smokers completed the brief Questionnaire of Smoking Urges (QSU brief; Cox et al. 2001), which distinguishes two subscales: strong desire to smoke and relief from negative effects. To measure impulsiveness, the Barratt Impulsiveness Scale, version 11 (Patton et al. 1995) was used, distinguishing the following six first-order factors: attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness. Furthermore, participants completed the Beck Depression Inventory (BDI) to assess mood (Beck et al. 1996) as well as the Decision Balance Scale for smoking (DBS; Velicer et al. 1985) to measure motivational (pros) and cognitive aspects (cons) of smoking (again, in ex-smokers in retrograde perspective).

Experimental task

A zoom version of the AAT was developed to measure implicit ApB. The paradigm required participants to push or pull a joystick (Logitech Attack TM 3) in response to the format of the cue (landscape or portrait) in which 50 % of the cues contained a smoking picture cue and 50 % contained a neutral picture cue (see Fig. 1 for a smoking avoidance trial). A picture format to response assignment was counterbalanced, with half of the participants pulling the joystick for landscape and pushing it for portrait cues, and vice versa. Participants had to respond to a picture within 3 s. Pulling and pushing the joystick increased and decreased the size of the cue, respectively. After 20 practice trials, 112 test trials were presented in three blocks, in which the distribution of stimulus content and image format was equal. There were 46 smoke-related cues and 46 color- and shape-matched neutral cues appearing pseudorandomly over the experiment, maximally allowing three cues with similar content or format in a row. Smoking cues consisted of individuals smoking cigarettes and close-ups of cigarettes or cigarette packs. The majority of cues were used in previous studies (e.g., Janes et al. 2010), whereas others were collected specifically for this experiment. Neutral cues were individuals holding matched items (such as pens or chop sticks) in their hands as well as close-ups of these items. Cues were presented

against a black background and did not differ in luminance ($t(91) = 1.29$, $p > 0.05$), analyzed with an adapted script of the MATLAB SHINE Toolbox (Willenbockel et al. 2010). The experiment was run on a computer with a 17-in. LCD monitor, 60 Hz of refresh rate, and a resolution of 1,440 × 900 pixels. Stimulus presentation and the recording of response time were accomplished using MATLAB (r2010a; MathWorks Company) and Psychtoolbox v3 (Brainard 1997).

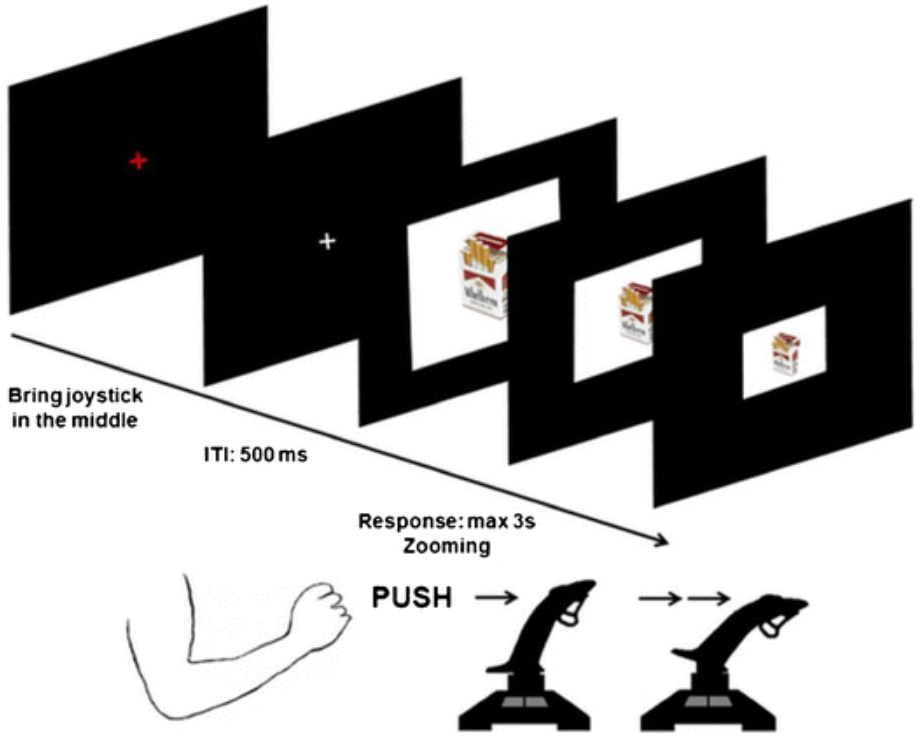

Fig. 1 Example of an avoidance trial of a smoking cue in the approach avoidance task, in which the cue zooms out

Statistical analyses

Responses that were missed or incorrect and RTs shorter than 300 ms or longer than three standard deviations (SDs) above the mean were discarded based on each participant's performance. RTs were measured from the onset of stimulus presentation until the joystick reached a maximum (push) or minimum (pull) position. Median RTs were used to calculate individual ApB scores, since they are less sensitive to outliers than mean scores (Cousijn et al. 2011; Rinck and Becker 2007; Wiers et al. 2009, 2010). For each participant, we calculated four RT scores for pulling and pushing smoking and neutral stimuli. Of these, ApB scores were calculated by subtracting median scores of pushing and pulling RTs (RTpush − RTpull) for each of the two stimulus types separately (see, e.g., Cousijn et al. 2011). Positive ApB scores indicate an approach bias (i.e., tendency to pull faster than push an image), whereas negative ApB scores indicate an avoidance bias (i.e., faster push than pull). Normal distributions of the four summary variables (smoking push, smoking pull, neutral push, and neutral pull) were tested with the Kolmogorov–Smirnov test. To test whether overall median RTs and error rates differed over smoking status, two separate one-way ANOVAs were performed with either overall median RTs or error rates as within-subject factor and group as between-subject factor. Moreover, a 2 (response type) × 2 (image type) × 3 (group) mixed ANOVA was performed to test whether the response type had an effect on ApB scores over groups.

To test for main effects of movement, a 2×3 mixed-factor ANOVA was performed, with movement (RTs push/RTs pull) as within-subject factor and group (smokers/ex-smokers/never-smokers) as between-subject factor. Then, since ApB scores were our variables of interest, a 2×3 mixed-factor ANOVA on ApB scores was used, with image type (smoking/ neutral) as within-subject factor and group (smokers/ex-smokers/never-smokers) as between-subject factor. Post hoc group comparisons on ApB scores were performed with two-way two-sample t tests. Because of specific hypotheses for smoking ApB scores being larger in smokers than in never-smokers and ex-smokers, one-way two-sample t tests were used for these two contrasts. Correlations between ApB scores, smoking characteristics, nicotine dependence, craving scores, and impulsivity scores were performed by means of bivariate Pearson's correlations.

Results

Sample characteristics

The groups did not differ in age, gender, alcohol usage, intelligence, years of education, or BDI scores (see Table 1 for demographic and smoking-related characteristics). Smokers and ex-smokers did not differ in the amount of cigarettes smoked per day, smoking duration, pack years, nor in motivational aspects of smoking on the DBS. However, there was a significant difference in FTND, with smokers being more tobacco-dependent than ex-smokers used to be ($t(42) = -2.78$, $p = 0.008$), which may be a bias of the retrospective nature of the report in ex-smokers. Moreover, there were no group differences on BIS impulsiveness scores (see Table 1).

Approach bias scores in smokers, ex-smokers, and never-smokers

Group comparison

Homogeneity of variance assumption was not violated for any of the variables ($p > 0.01$, see Table 1). Task difficulty was low, and exclusion of errors and trial outliers left 95.8 % of trials for further analyses. All variables were distributed normally ($p > 0.25$). Results of the AAT for the three groups are demonstrated in Fig. 2. Both median RTs ($F(2, 61) = 0.14$, $p = 0.87$, ns) and mean error rates ($F(2, 61) = 0.20$, $p = 0.82$, ns) did not differ between groups. Moreover, there was no effect of response type on approach biases over the three groups: neither the response type × image type ($F(1, 58) = 0.04$, $p = 0.84$, ns) nor the response type × image type × group ($F(1, 58) = 1.53$, $p = 0.23$, ns) revealed a significant interaction effect. The 2×3 mixed-factor ANOVA on median RTs showed a main effect of movement ($F(1, 61) = 5.47$, $p = 0.023$, $\eta 2 = 0.082$), with pulling cues being faster ($M \pm SE = 887.61 \pm 20.45$ ms) than pushing cues ($M \pm SE = 906.99 \pm 21.33$ ms).

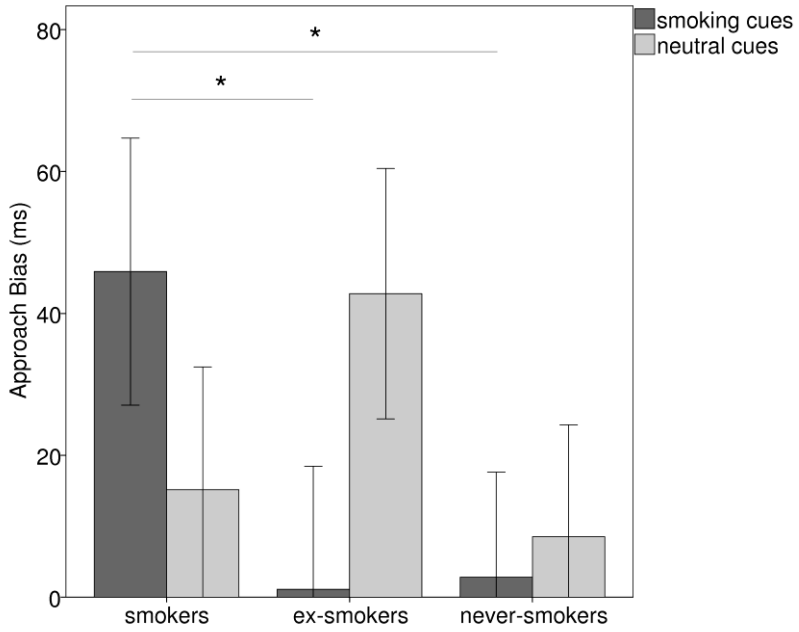

Fig. 2 Mean ApB score for smoking and neutral cues in smokers, ex-smokers, and never-smokers. Positive scores show faster tendencies to approach than avoid cues. Smoking ApB was larger in smokers compared to never-smokers and ex-smokers (both, $p < 0.05$). Smokers' ApB for smoking cues and ex-smokers' ApB for neutral cues were larger than 0 (both, $p < 0.05$).

For ApB scores, the 2 (image type) × 3 (group) mixed ANOVA revealed an interaction effect of image type × group ($F(1, 61) = 3.67$, $p = 0.031$, $\eta^2 = 0.107$). There were no significant main effects. In line with our hypothesis, smokers had stronger smoking ApB scores than never-smokers ($t(42) = 1.74$, $p = 0.044$; smokers: M ± SE = 45.90 ± 18.82 ms; never-smokers: M ± SE = 2.83 ± 14.82 ms), whereas ApB scores for neutral cues did not differ between the groups ($t(42) = 0.28$, $p = 0.78$, ns). Moreover, smokers had higher smoking ApBs than ex-smokers ($t(42) = 1.72$, $p = 0.047$; smokers: M ± SE = 45.90 ± 18.82 ms; ex-smokers: M ± SE = 1.13 ± 17.33 ms), but there was no difference in neutral bias scores ($t(42) = -1.11$, $p = 0.27$). Neither smoking ApB scores were different between ex-smokers and never-smokers ($t(38) = 0.75$, $p = 0.94$, ns; ex-smokers: M ± SE = 1.13 ± 17.33 ms; never-smokers: M ± SE = 2.83 ± 14.82 ms) nor were neutral ApB scores ($t(38) = 1.45$, $p = 0.16$, ns; ex-smokers: M ± SE = 42.78 ± 17.64 ms; never-smokers: M ± SE = 8.52 ± 70.54 ms).

Correlations

Smoking ApB and neutral ApB were correlated positively over all groups ($R = 0.344$, $p = 0.005$). Three participants in the smoking group did not fill out the QSU questionnaire, which left 21 smokers for craving analyses. As hypothesized, smokers' ApB scores for smoking cues correlated positively with total QSU craving scores ($R = 0.56$, $p = 0.008$). The correlation was particularly apparent for the subscore QSU strong desire to smoke ($R = 0.50$, $p = 0.022$), but not with subscore QSU relief from negative effect ($R = 0.37$, $p = 0.10$). Ex-smokers' ApB scores for smoking cues, although not deviant from 0 but with large variance (M ± SD = 1.13 ± 77.48, range −182.5 to 156 ms), correlated positively with smoking duration ($R = 0.55$, $p = 0.012$), with pack years ($R = 0.55$, $p = 0.013$), and the amount of cigarettes smoked per day by trend ($R = 0.44$, $p = 0.053$), but not with duration of abstinence ($R = 0.11$, $p = 0.635$). None of the groups showed

a correlation between smoking bias and the FTND score ($p > 0.16$), nor with BIS scores ($p > 0.17$).

Since ex-smokers and controls did not report to crave cigarettes at all (i.e., all QSU scores were 0), we did not conduct correlations with this measure for these groups. In ex-smokers, BIS scores of cognitive instability impulsivity, measuring thought insertion and occurrence of running thoughts, correlated negatively with neutral ApB scores ($R = -.53$, $p = 0.016$), with higher ApB scores correlating with lower cognitive instability impulsiveness. None of the correlations with other factors of BIS were significant ($p > 0.10$).

Discussion

In this study, automatic action tendencies towards smoking cues were studied in smokers, ex-smokers and a never-smoking control group, as measured with the AAT (Cousijn et al. 2011; Rinck and Becker 2007; Wiers et al. 2009, 2010, 2011; Zhou et al. 2012). Compared to never-smokers and ex-smokers, smokers revealed an approach bias towards smoking-related images, which, as predicted, correlated with smokers' QSU craving scores.

The first result suggests that, for smokers, smoking cues are not only attention grabbing as has been shown in previous attentional bias paradigms (Mogg et al. 2003; Waters et al. 2003a), but are also eliciting automatic action towards them. This study has been the first to use the AAT for examining approach tendencies for smoking cues in a heavy-smoking group versus a never-smoking control group. Approach tendencies assessed with the AAT have been described in other addictions—in alcohol-dependent patients (Ernst et al. 2012; Wiers et al. 2011), heroin abusers (Zhou et al. 2012), and in cannabis users (Cousijn et al. 2011)—suggesting a common underlying pathway for approaching drug cues in addiction. Moreover, it has previously been shown that cigarette smokers exposed to smoking cues demonstrated increased activation in limbic brain areas (Nestor et al. 2011) as well as in action-related brain areas (Wagner et al. 2011). These findings support the hypothesis that mesolimbic neuroadaptations underlie the automatic approach bias for drug cues, as proposed by the incentive salience theory of addiction (Robinson and Berridge 1993, 2003). The positive correlations of smoking approach tendencies with explicit craving scores in smokers are also in accordance with the incentive salience theory that suggests that sensitization and craving are related. Nonetheless, this correlation has not been described in previous ApB literature on the AAT in addicted populations, neither in alcohol-dependent (Wiers et al. 2011) and heroin-dependent patients (Zhou et al. 2012) nor in heavy cannabis users (Cousijn et al. 2011). A possible explanation for this is that the time in between drug taking is generally shorter in smokers compared to other drug users. This may lead to higher levels of craving after a short period of time. Moreover, the alcohol- and heroin-dependent patients in previous studies were in treatment programs and already abstinent of the drug for several months, which may have influenced explicit craving ratings.

Despite the positive relation of ApB to craving in smokers, we did not find the hypothesized correlation with smoking characteristics (e.g., cigarettes per day and pack years). A reason for this may be that only heavy smokers who smoked more than 15 cigarettes per day participated in the study, hence reaching a ceiling effect in dependency. Conversely, smoking ApBs in ex-smokers did not correlate with craving (none of the ex-smokers reported to crave at all) but positively with pack years and smoking duration. In other words, ex-smokers who smoked more and longer in their past still demonstrated relatively strong approach tendencies for smoking.

Given these results, it is possible that incentive salience to cues is present in most active users but decreases over abstinence. This suggests that further research clarifying the relationships between smoking cessation, ApBs, and craving could reveal interesting results. Importantly, although these first findings on smokers' ApB are supporting the incentive salience theory of addiction and make it likely that ApB is the result of Pavlovian conditioning, the study design does not rule out that other mechanisms also play a role in ApB. It could be that approach tendencies in drug abusers represent habitual responses to drug cues, or goal-directed behavior in which the approach tendencies were to be controlled by the expectancy of the rewarding outcome of the drug (Watson et al. 2012). Future studies are necessary to provide more insight into the mechanism of the ApB to drug cues.

The second result also confirmed our hypothesis: ex-smokers were expected to reveal a diminished approach bias for smoking cues, which was shown. Ex-smokers' smoking ApBs were significantly smaller than smoking ApBs of current smokers. Although the present study was the first to study ApBs in ex-smokers, the results are in line with a previous study on attentional bias (Munafo et al. 2003), that likewise revealed no difference in smoking cue vigilance between ex-smokers and never-smokers on a visual probe task. Still, other studies did not find a behavioral effect of diminished attentional bias in ex-smokers (Munafo and Johnstone 2008; Munafo et al. 2005; Nestor et al. 2011). Nevertheless, the results suggest that if mesolimbic neuroadaptations indeed underlie the ApB in current smokers, these neuroadaptations are not permanent but can reverse after cessation. In this way, our findings do not confirm Robinson and Berridge's prediction that neuroadaptations and senzitization are stable over abstinence. Further, the incentive salience theory also predicts craving and sensitization to be related (Robinson and Berridge 1993). In our study, none of the ex-smokers reported craving. It could, therefore, be that automatic biases decrease over abstinence as a result of decreased craving or decreased rewarding effects of drugs. Or, ex-smokers found strategies to diminish their approach behavior to smoking cues, as suggested by dual process models of addiction (e.g., Wiers et al. 2007). The groups did not differ in self-reported motivation to smoke (ex-smokers filled out these motivations in retrospect, on when they were still smoking) and, although hypothesized, neither in BIS impulsiveness scores. Smoker status as well as the absence of smoking ApB could, hence, not be explained by (previous) drug motivations or impulsiveness personality traits.

Some limitations of the study have to be considered. First, smokers and ex-smokers differed not only in their smoking status but also in their FTND scores, i.e., tobacco dependency scores. FTND scores were lower in ex-smokers compared to smokers, despite equal scores for smoking duration and number of cigarettes smoked. Since ex-smokers filled out the FTND questionnaire retrospectively, one explanation for the group difference in tobacco dependency is that memories of tobacco dependence were recollected less well. Moreover, if there was a true difference in addiction severity, it could not explain a double dissociation between smokers and ex-smokers. If the group difference was driven by the confounding factor severity only, one would expect the ex-smokers to show an intermediate effect between smokers and never-smokers rather than an effect double in size. A second limitation is that, besides excluding participants who sought treatment, ex-smokers were not asked about the way in which they quit their smoking behavior. To inform the approach bias in ex-smokers, future studies should ask ex-smokers whether they experienced withdrawal feelings, substitution behavior, or weight gain. Third, explicit ratings of valence of arousal for the stimuli were not assessed, which could have been interesting to correlate with bias scores as well as craving scores. It is expected that arousal for smoking cues is high in smokers, but that ex-smokers do not explicitly rate neutral cues as arousing. Last, in

previous studies on automatic biases in smoking, bias scores have been shown to be higher in light smokers than in heavier smokers (Hogarth et al. 2003; Waters et al. 2003a). In these studies, bias scores turned out to be absent in individuals smoking more than 20 cigarettes per day. In our design, however, we only included heavy smokers. It is therefore possible that approach bias scores could be higher in smokers when lighter smokers were also included.

In summary, the study provides evidence for approach motor tendencies for smoking cues in smokers, but not in ex-smokers. ApB scores in smokers might be a relevant objective measure for motivational aspects of drug dependence. Since ApBs were shown to be a predictor for continuation of drug use in cannabis smokers (Cousijn et al. 2011) and retraining approach biases in bias modification training programs lead to lower relapse rates and improved treatment outcomes in alcohol-dependent patients (Eberl et al. 2013; Wiers et al. 2011), ApBs could be of clinical value in drug addiction. Individualized therapies could be developed for smokers who wish to quit. For example, when ApBs are high, therapies could specifically target cue reactivity and automatic processes and motivate smokers to perform cognitive training aimed at this purpose (Wiers et al. 2013).

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Appendix

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Conflict of interest
None

Footnotes
[1] Excluding these two ex-smokers from the analyses still results in a significant interaction effect of image type × group ($F(1, 59) = 5.10$, $p = 0.009$, $\eta 2 = 0.147$) on the 2 (image type) × 3 (group) mixed ANOVA.

EXPERIMENT II – NEURAL CORRELATES OF ALCOHOL-APPROACH BIAS IN ALCOHOL ADDICTION: THE SPIRIT IS WILLING BUT THE FLESH IS WEAK FOR SPIRITS

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Abstract
Behavioral studies have shown an alcohol approach bias in alcohol-dependent patients: the automatic tendency to faster approach than avoid alcohol compared to neutral cues, which has been associated with craving and relapse. Although this is a well-studied psychological phenomenon, little is known about the brain processes underlying automatic action tendencies in addiction. We examined 20 alcohol-dependent patients and 17 healthy controls with functional magnetic resonance imaging (fMRI), while performing an implicit approach avoidance task (AAT). Participants pushed and pulled pictorial cues of alcohol and softdrink beverages, according to a content-irrelevant feature of the cue (landscape/portrait). The critical fMRI contrast regarding the alcohol approach bias was defined as (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink). This was reversed for the avoid alcohol contrast: (avoid alcohol>approach alcohol) > (avoid softdrink>approach softdrink). In comparison with healthy controls, alcohol-dependent patients had stronger behavioral approach tendencies for alcohol cues than for softdrink cues. In the approach alcohol fMRI contrast patients showed larger blood-oxygen-level dependent (BOLD) responses in the nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC), regions involved in reward and motivational processing. In alcohol-dependent patients alcohol craving scores were positively correlated with activity in the amygdala for the approach alcohol contrast. The dorsolateral prefrontal cortex (dlPFC) was not activated in the avoid alcohol contrast in patients versus controls. Our data suggest that brain regions that play a key role in reward and motivation are associated with the automatic alcohol approach bias in alcohol-dependent patients.

Introduction

Addiction is characterized by habitual drug-use despite negative consequences and by high rates of relapse, even though the addicted person is often aware of the harm (Stacy and Wiers, 2010). Recent theories suggest reward-related learning to be important for the development of addiction (Hyman *et al*, 2006; Wrase *et al*, 2002): a transition occurs from voluntary to impulsive use, in which cues associated with the drug increase in incentive salience (Robinson and Berridge, 1993, 2003). Drug cues then automatically trigger drug-like approach responses (Robinson *et al*, 1993, 2003). Dual process models of addiction propose an imbalance between these strong automatic "approach"-oriented processes and a suboptimal functioning of cognitive control processes (Bechara, 2005; Gladwin *et al*, 2011). This imbalance may explain the paradoxical conflict that characterizes addiction: urges to take the drug that the individual fails to control despite an explicit desire to quit.

Previous research has demonstrated that drug-dependent individuals exhibit an automatically activated tendency to approach rather than to avoid drug cues relative to neutral cues (i.e. drug approach bias; Cousijn *et al*, 2011; Ernst *et al*, 2012; Wiers *et al*, 2013; Zhou *et al*, 2012). The drug approach bias is likely to reflect an embodied motor reaction towards drug cues and has been positively related to subjective rates of drug craving (Wiers *et al*, 2013). Moreover, bias modification training schemes, in which drug users learn to avoid drug cues in a joystick paradigm, have been shown to reduce relapse rates up to 13% in alcohol-dependent patients one year after training (Eberl *et al*, 2012; Wiers *et al*, 2011). These findings highlight the clinical relevance of approach bias in drug-use. However, neural correlates associated with the drug approach bias remain largely unknown.

The incentive-sensitization theory of addiction suggests fronto-limbic neuroadaptations to underlie the drug approach bias (Robinson *et al*, 2003). Many drugs of abuse (e.g., alcohol, nicotine or cocaine) directly or indirectly trigger the release of dopamine from the ventral tegmental area (VTA), projecting to fronto-limbic structures such as the nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC; Heinz *et al*, 2009; Hyman and Malenka, 2001). Since dopamine signals motivational relevance, with every puff, drink or shot, Pavlovian conditioned associations between drug cues and reward are formed and encoded in the amygdala (Baler and Volkow, 2006; Heinz *et al*, 2009). In this way, drug cues acquire incentive sensitization and consequently engender approach behavior (Robinson *et al*, 1993, 2003).

Human functional magnetic resonance imaging (fMRI) studies have shown that when drug-users passively view drug cues, blood-oxygen-level dependent (BOLD) signal (hereafter: activity) in the fronto-limbic reward circuit increases (Heinz *et al*, 2009; Schacht *et al*, 2013). Key brain areas that activate in drug-users are the NAcc, mPFC, dorsolateral prefrontal cortex (dlPFC) and amygdala (Heinz *et al*, 2009; Schacht *et al*, 2013). However, despite the evidence for fronto-limbic involvement in drug-cue reactivity the precise role of these areas remains unclear. The NAcc, mPFC and amygdala have been associated with bottom-up motivational aspects of cue reactivity (Braus *et al*, 2001; Hare *et al*, 2009; Heinz *et al*, 2009; Wrase *et al*, 2007), reward processing (Kahnt *et al*, 2010; Koob and Volkow, 2010; Park *et al*, 2011), subjective drug craving and relapse (Beck *et al*, 2012; Childress *et al*, 1999; Grusser *et al*, 2004; Hayashi *et al*, 2013; Heinz *et al*, 2004; Volkow *et al*, 2004). The dlPFC has been shown to be structurally and functionally impaired in drug addiction, and may be related to suboptimal cognitive control (Baler *et al*, 2006; Bechara, 2005; Hayashi *et al*, 2013; Jentsch and Taylor, 1999; Park *et al*, 2010). Previous approach/avoidance studies on emotional processing showed that dlPFC is more

active when stimulus and response are incongruent (approach sad faces) than congruent (approach happy faces; Roelofs *et al*, 2009; Volman *et al*, 2011). If patients indeed have an alcohol approach bias (congruent), the dlPFC would be expected to be active while avoiding alcohol cues (incongruent). Alternatively, when patients lack the control to avoid alcohol cues, one would expect decreased dlPFC activation for avoiding alcohol cues. How these antagonistic processes of motivation and control underlie automatic approach tendencies for alcohol as yet remains unknown.

In the current study, we measured the neural correlates of the automatic alcohol approach bias using fMRI. Abstinent alcohol-dependent patients and healthy controls performed an implicit AAT in an fMRI scanner. As such, this is the first study that investigates the neural correlates of the alcohol approach bias in alcohol dependence using fMRI. Participants pushed and pulled pictorial cues of alcohol and softdrink beverages using a joystick. Compared with controls, patients were hypothesized to faster pull than push alcohol stimuli compared to softdrink stimuli. For the fMRI alcohol approach bias interaction (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink) we expected increased activity in NAcc, mPFC and amygdala, areas previously associated with reward and motivational processing. Subjective craving scores of alcohol-dependent patients were hypothesized to correlate positively with the alcohol approach bias-related activity in these regions. Lastly, we investigated whether patients showed either greater or reduced dlPFC activity than healthy controls in a reverse avoid alcohol contrast (avoid alcohol>approach alcohol) > (avoid softdrink>approach softdrink), indicating enhanced or reduced inhibitory control respectively.

Methods

Participants and instruments

The Ethical Committee of the Charité, Universitätsmedizin Berlin approved the study. Thirty seven right-handed male subjects participated: 20 alcohol-dependent inpatients (*M*=44.3 years (*SD*=7.98), range=26-55) and 17 healthy control subjects (*M*=42.1, *SD*=8.32, range=22-53). The groups did not differ in mean age and years of education (Table 1). Controls were recruited via online advertisements. Exclusion criteria for all participants were a history of neurological dysfunctions, axis I psychiatric disorders according to DSM-IV criteria other than alcohol dependence in the alcohol-dependent group (M.I.N.I. plus, an International Neuropsychiatric Interview; Sheehan *et al*, 1998) and intake of psychoactive medication. Controls did not fulfill criteria of (a history of) drug abuse and dependence, except tobacco. For controls, potential participants with scores above 8 on the Alcohol Use Disorder Identification Test (AUDIT; Saunders *et al*, 1993) were excluded, as screened in a telephone interview prior to the experiment. Patients were recently detoxified (< 6 months; *M*=53.40 days, *SD*=49.51), had been suffering from alcohol dependence for 16.6 (*SD*=8.5 years, range 1–30), underwent 3.9 (*SD*=6.7) previous detoxifications (range 0–25) and scored 16.4 (*SD*=8.4) on the Alcohol Dependence Scale (Skinner and Allen, 1982). Smokers were abstinent from tobacco at least 1.5 hours before scanning, in order to decrease direct effects of nicotine on the BOLD signal (Jacobsen *et al*, 2002). All patients expressed the desire to remain abstinent from alcohol.

In order to assess lifetime history of alcohol and drug abuse for both groups, we interviewed participants on the Life Time Drinking History scale (Skinner and Sheu, 1982). Alcohol craving was assessed with the Desire for Alcohol Questionnaire (DAQ; Love *et al*, 1998). Furthermore, participants completed Matrix Reasoning of the Wechsler Adult Intelligence Scale (Kaufman and

Lichtenberger, 2006) as a proxy for general intelligence and the Spielberger's State-Trait Anxiety Questionnaire (STAI) to evaluate state and trait anxiety (Spielberger *et al*, 1983).

Approach avoidance task description and subjective rating

A zoom version of the approach avoidance task (AAT), optimized for MRI, was used (Figure 1). Participants pushed or pulled an MRI-compatible joystick (Fiber Optic Joystick, Current Designs), in response to the format of the cue (landscape or portrait). After 20 practice trials, 160 test trials were presented over 4 blocks, in which each picture was approached and avoided once. Picture format to response assignment was counterbalanced, with half of the participants pulling the joystick for landscape and pushing it for portrait cues, and vice versa. For optimal approach and avoidance resemblance (Rinck and Becker, 2007), the AAT used here was developed with a zooming feature: moving the joystick increased and decreased the size of the cue. Participants had to respond to a picture within 2 seconds. Inter-trial intervals (ITIs) were 4, 6 or 8 seconds, distributed hyperbolically (Miezin *et al*, 2000). A set of 40 alcohol and 40 softdrink images was used, previously matched for drink familiarity and for arousal in an independent male, social drinking German sample (N=20). Images (660×660 pixels) were presented in a white frame (900×660 pixels landscape and 660×900 pixels portrait format), against a black background. The task was programmed in MATLAB (r2010a; MathWorks Company) and Psychtoolbox v3 (Brainard, 1997). After scanning, all pictures were rated for familiarity ("How familiar is this drink to you?"), arousal ("How much does this drink move you?") and valence ("How positive or negative is this drink to you?"), on a five-point Likert scale.

fMRI acquisition and preprocessing

Stimuli were presented in an event-related design (4 runs of 40 trials) in a 3 Tesla MRI scanner (MAGNETOM Trio, TIM-Technology; Siemens, Erlangen, Germany), equipped with a 12-channel head coil. A standard T2- weighted echo planar imaging (EPI) sequence was used with the following parameters: descending, repetition time 2 s, echo time 25 ms, flip angle α 80°, 64×64 pixels in-plane resolution, 34 slices, slice thickness 3 mm, voxel dimensions 3×3×3 mm^3, with a 0.75 mm gap between slides, field of view 192×192 mm^2. In each of the four runs, 163 images were acquired. To improve functional sensitivity in the mPFC, the acquisition plane was tilted 25 degrees clockwise from anterior-posterior commissure (Deichmann *et al*, 2003).

Functional data analysis was performed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). During preprocessing, scans were spatially realigned, slice-time corrected and normalized to the standard Montreal Neurological Institute (MNI) EPI template. Smoothing was performed with an 8 mm full width at half-maximum (FWHM) Gaussian kernel. None of the participants moved more than 2 mm or 2 degrees within runs.

Statistical analysis

Responses that were missed or incorrect and response times (RTs) longer than 3 *SD*s above the mean were discarded based on each participant's performance. RTs were computed as the time required from the onset of stimulus presentation until the joystick reached a maximum or minimum position. Approach tendencies were calculated by subtracting median RT scores of pushing minus pulling pictures for each drink type. Positive approach tendencies indicate faster approaching than avoiding an image type, whereas negative approach tendencies indicate faster avoidance than approach. A 2×2 mixed ANOVA on approach tendencies was calculated, with drink type (alcohol/softdrink) as within-subject factor and group (alcohol-dependent /healthy control) as between-subject factor. Post-hoc group comparisons on separate approach tendencies

(alcohol/softdrink) were performed with two-sided two-sample *t*-tests. The behavioral alcohol approach bias RT score was defined as the difference score of approach tendency for alcohol minus approach tendency for softdrink. Pearson's correlation was calculated between the behavioral alcohol approach bias and DAQ alcohol craving.

For fMRI data, there were five regressors per subject: alcohol push, alcohol pull, softdrink push, softdrink pull and missed trials. Single trials were modeled with the trial's RT as duration of the event and convolved with the hemodynamic response function. The six realignment parameters were included as regressors-of-no-interest. Temporal filtering of 128 s was used.

The following contrasts were calculated per subject: (1) (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink) for the approach alcohol contrast and (2) the reverse (avoid alcohol>approach alcohol) > (avoid softdrink>approach softdrink) for the avoid alcohol contrast. On the second level, both contrasts were compared between groups using a two-sample *t*-test. We created four regions of interest (ROIs), based on our a-priori hypotheses (Figure 2). Both the NAcc and amygdala ROIs were defined by the bilateral NAcc and amygdala using the human anatomical WFU Pickatlas (Maldjian *et al*, 2003). Since mPFC and bilateral dlPFC are anatomically not clearly defined, two functional ROIs of these brain areas were downloaded from an online atlas of functional ROIs (Shirer *et al*, 2012). ROIs were used for small-volume correction (SVC) of the results, with a significance threshold of $p<.05$, family wise error corrected (FWE).

For post-hoc analyses two approach tendency contrasts were calculated on the first level: (1) (approach alcohol>avoid alcohol) and (2) (approach softdrink>avoid softdrink). These contrasts were compared between groups using two-sample *t*-tests, masked with our a-priori defined ROIs.

To test whether length of abstinence was negatively related to activity in our ROIs, regression analyses within these ROIs with length of abstinence as a regressor were performed in alcohol-dependent patients only.

To identify correlations with DAQ craving scores and alcohol approach bias-related brain activations in alcohol-dependent patients, we performed a regression analysis on the approach alcohol contrast, with DAQ scores as a regressor. Results of correlations were FWE-corrected (SVC) for our ROIs (NAcc, mPFC and amygdala).

Results

Behavioral assessment and subjective ratings

Groups did not differ in years of education, body mass index (BMI), Wechsler Adult Intelligence Scale **(**WAIS) intelligence scores or in anxiety trait (STAI-T) and state (STAI-S) scores (Table 1). There were more smokers in the alcohol-dependent group (N=20, 100%) compared to the control group (N=6, 28.3%; χ^2=7.54, p=.006). We did however not include smoking as a covariate since smoking behavior was related to lifetime alcohol consumption (R=.58, p=.007; also when corrected for age: R=.58, p=.007) and DAQ craving scores (R=.45, p=.047) in alcohol-

dependent patients. Consequently, including smoking as a covariate may remove variance explained by drinking behavior.[1]

DAQ alcohol craving ratings were higher in alcohol-dependent patients (M=14.3, SD=6.7) compared to healthy controls (M=4.88, SD=4.4; $t(35)$=3.55, p=.001). Picture ratings (familiarity, valence and arousal) for both alcohol and softdrink cues did not differ between groups (all p>.13).

For the AAT, all RT variables, both separate approach tendencies (alcohol/softdrink) and the overall alcohol approach bias score were distributed normally (Kolmogorov-Smirnov test: all p>.12). The assumption of homogeneity of variance was met in all cases (Levene's test for Equality of Variance: all p>.52). Mean error rate was 1.71% (SD=1.95) and error rates did not differ between groups ($t(35)$=.49, p=.63).

As hypothesized, for behavioral approach tendencies there was a significant interaction effect between drink type × group ($F(1,34)$=9.99, p=.003, η^2=.22; Figure 3). Post-hoc t-tests revealed that patients had greater approach tendencies for alcohol cues (M=48.10 ms, SD=54.35) compared to healthy controls by trend (M=12.71 ms, SD=54.61; $t(35)$=1.97, p=.057). In contrast, approach tendencies for softdrink cues did not differ between groups (t(35)=-.92, p=.37).

The behavioral alcohol approach bias did not correlate with DAQ alcohol craving scores, either in alcohol-dependent patients (r=.17, p=.48), or in healthy controls (r=-.18, p=.49).

fMRI Results

Approach alcohol

For the main contrast of interest (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink), alcohol-dependent patients showed a higher BOLD response in the NAcc area (peak in MNI space [x,y,z]=[15,5,-8]); t=3.54, p<.05, FWE) and the mPFC (peak=[0,59,7]); t=4.43, p<.05, FWE) compared to healthy controls (Figure 4). The amygdala was not more strongly activated in patients compared to controls (bilateral; p>.05, FWE), even at a more liberal threshold of p<.005 uncorrected. Although the dlPFC was not more activated in patients than controls with the threshold of p<.05, FWE, a cluster in the left dlPFC survived the exploratory, more liberal threshold of p<.005 uncorrected.

Post-hoc t-tests on separate approach tendency contrasts revealed that alcohol-related activity (approach alcohol>avoid alcohol) did not differ between groups in the NAcc and mPFC, (p>.005 uncorrected). Approach tendency-related activity for softdrink cues (approach softdrink>avoid softdrink) was larger in healthy controls than alcohol-dependent patients, both in the NAcc (peak=[9,8,-8]; t=3.08, p<.05, FWE) and mPFC (peak=[-12,56,7]); t=5.15, p<.05, FWE).

Within patients, length of abstinence was not correlated with the approach alcohol contrast within our ROIs (p>.05 FWE and p>.005 uncorrected).

[1] An exploratory analysis with smoking behavior as a covariate in the main group analysis revealed that whereas results on NAcc (p<.05, FWE) and dlPFC (lack of effect at p>.05, FWE) in both the approach and avoid contrast did not change, activity in the mPFC did not reach significance when including smoking as a covariate (p>.05, FWE).

Avoid alcohol
In the reverse avoid alcohol contrast (avoid alcohol>approach alcohol) > (avoid softdrink>approach softdrink), no suprathreshold activity was reached in the dlPFC (bilateral; p>.05, FWE) in patients versus controls. Moreover, an additional analysis with a more liberal threshold of p<.005 (uncorrected) did not reveal suprathreshold activity.

Correlation of craving scores with alcohol approach bias-related activity in alcohol-dependent patients
Alcohol-dependent patients' DAQ craving scores correlated positively with activity in the amygdala for the approach alcohol contrast (peak=[30,-7,-11]); t=4.25, p<.05, FWE; Figure 5). There were no positive correlations between alcohol craving and activity in the NAcc or mPFC, even at p<.005 uncorrected.

Results of whole brain-analyses are reported in supplementary Table 1 (S1).

Discussion
The current study shows that in comparison to healthy controls, alcohol-dependent patients had stronger behavioral approach tendencies for alcohol cues than for softdrink cues. At the neural level, the alcohol approach bias interaction of drink type (alcohol vs. softdrinks) × movement (approach vs. avoid) was associated with stronger brain response in both NAcc and mPFC, areas that have previously been shown to play a role in alcohol cue reactivity, reward processing and the motivational value of stimuli (Grusser *et al*, 2004; Hare *et al*, 2009; Heinz *et al*, 2009; Kahnt *et al*, 2010; Park *et al*, 2011). Here we show that these areas are more active in patients versus controls while approaching versus avoiding alcohol cues, relative to softdrink cues. This extends previous studies, which mostly involved passive viewing of alcohol cues (Heinz *et al*, 2009; Schacht *et al*, 2013). However, no strong effects were found in the dlPFC. Thus, we did not find direct support for enhanced or decreased neural inhibitory control while patients were avoiding alcohol. The results suggest that differences in the motivational reward system, rather than a less active control system, underlie automatic action tendencies to alcohol in alcohol dependence.

The main findings support incentive sensitization models of addiction that propose fronto-limbic neuroadaptations to underlie the automatic approach bias to drug cues in addicted individuals (Robinson *et al*, 1993, 2003). The NAcc has been shown to be responsive to alcohol cue reactivity in alcohol-dependent patients (Braus *et al*, 2001; Heinz *et al*, 2009; Wrase *et al*, 2007) and regulates drug sensitization in animals (Abrahao *et al*, 2011). The mPFC is hypothesized to code subjective value-signals important for goal-directed decision making (Hare *et al*, 2009; Kahnt *et al*, 2010; Park *et al*, 2011) and has been related to the attribution of incentive salience to alcohol cues (Grusser *et al*, 2004). Recently, activity in the mPFC was shown for the cannabis approach bias in both cannabis users and non-smoking controls (Cousijn *et al*, 2012). Moreover, a recent near-infrared spectroscopy study demonstrated that the neighboring orbitofrontal cortex is active when alcohol-dependent patients approach alcohol cues (Ernst *et al*, 2012). Hence, the NAcc and mPFC may play important roles in the drug approach bias.

As expected alcohol-dependent patients reported higher subjective craving for alcohol compared with the control group. Although the amygdala was not activated in the main approach alcohol contrast in patients versus controls, alcohol approach bias-related brain activity in the amygdala correlated positively with alcohol craving scores in patients. This finding is in line with previous neuroimaging findings that also showed a positive relation between activity in the amygdala

while passively viewing alcohol cues and subjective craving (Childress *et al*, 1999; Koob *et al*, 2010). The amygdala plays a key role in Pavlovian conditioned learning and the formation and consolidation of emotional memories (Koob *et al*, 2010; Volkow *et al*, 2004). Drug craving may therefore lead to increased memories of the abused drug, or in reverse, approaching alcohol may trigger drug associations and memories that initiate craving. However, our results did not support the hypotheses that increased NAcc and mPFC were related to subjective craving in patients. It may therefore be that NAcc and mPFC are specific for automatic approach reactions rather than explicit subjective judgments of drug craving, whereas the amygdala is only activated in patients that are explicitly aware of their craving.

The dlPFC was neither more nor less active in our avoid alcohol contrast in patients versus controls, under the stringent threshold of $p<.05$ FWE. More activity in the dlPFC was expected in patients compared with controls, since previous studies found that the dlPFC is generally more active when stimulus and response are incongruent (Roelofs *et al*, 2009; Volman *et al*, 2011). In contrast, it may be that patients lack control to avoid alcohol and hence show reduced dlPFC activity in the avoid alcohol contrast. In the latter contrast, a cluster in the left dlPFC survived the exploratory, more liberal threshold of $p<.005$ uncorrected. Since this result is uncorrected only, it cannot be firmly interpreted. Thus, differences in dlPFC activation between groups cannot be excluded at this point (and neither can they be confirmed). Since alcohol-dependent patients were all clinic inpatients, it may be that avoiding alcohol cues was not incongruent for this population. This could explain why the dlPFC was not activated in the avoid alcohol contrast in patients compared to controls. Future studies could investigate whether neural correlates of the alcohol approach bias in social or hazardous drinkers for whom drinking is not (yet) problematic would involve dlPFC activity for avoiding alcohol. Moreover, in high-risk cannabis smokers, higher dlPFC activity during cannabis approach trials, but lower activity during cannabis avoidance trials were associated with decreases in cannabis problem severity six months later (Cousijn *et al*, 2012). Although these findings were obtained with a structurally different task, in which participants symbolically approach the drug in certain mini-blocks and avoid it in other mini-blocks, future studies could focus on alcohol approach bias-related dlPFC activity in relation to future addiction severity in alcohol-dependence.

Post-hoc *t*-tests revealed that the significant behavioral alcohol approach bias interaction was mainly driven by a trend-wise difference between groups in approach tendencies for alcohol cues rather than softdrink cues. That is, as hypothesized, behavioral approach tendencies for alcohol were larger in patients versus controls, whereas there was no detectable group difference for softdrink approach tendencies. In contrast, the interaction of BOLD responses in mPFC and NAcc was mainly driven by group differences in approach>avoid softdrink cues rather than approach>avoid alcohol cues. That is, patients showed significantly lower activity in mPFC and NAcc when approaching>avoiding softdrinks, but there were no significant between-group differences in BOLD responses when approaching>avoiding alcohol. It is, however, difficult to interpret the separate approach tendency contrasts in isolation from the alcohol approach bias interaction of drink type (alcohol vs. softdrinks) × movement (approach vs. avoid). Namely, there are methodological reasons to include a neutral category (softdrinks) to the main analysis. First, this allowed us to correct for general approach/avoid tendencies. For example, it may be that patients generally show reduced BOLD responses for approach tendencies of neutral stimuli, such as softdrinks. Second, this corrects for differences in visual feedback and motor movements between approach (zoom in/pull) and avoidance (zoom out/push) trials. Third, defining automatic drug biases as the difference between BOLD signals elicited by drug cues and neutral cues is in

line with previous fMRI research on the drug approach bias (Cousijn *et al*, 2012), the drug attentional bias (Janes *et al*, 2010; Vollstadt-Klein *et al*, 2011) and drug cue reactivity (Beck *et al*, 2012; Childress *et al*, 1999; Grusser *et al*, 2004; Heinz *et al*, 2004; Heinz *et al*, 2009; Wrase *et al*, 2007). Nevertheless, the between-group differences in the softdrink approach tendency contrast rather than for alcohol may well be meaningful. It may be that the alcohol approach bias is due to decreased motivational brain responses to naturally rewarding stimuli, such as softdrinks, rather than an increased motivational response to alcohol. This is in line with previous studies showing that addicted individuals demonstrate reduced reward-related activation to naturally rewarding stimuli compared to controls (Volkow *et al*, 2004; Wrase *et al*, 2007). In previous fMRI research on drug approach biases, drug attentional biases and drug cue reactivity, post-hoc tests exploring interactions have not usually been performed (for an exception, see Braus *et al*, 2001), nor have plots of the separate beta coefficients of alcohol/ neutral subscores been provided (Beck *et al*, 2012; Childress *et al*, 1999; Cousijn *et al*, 2012; Grusser *et al*, 2004; Heinz *et al*, 2004; Janes *et al*, 2010; Wrase *et al*, 2007; Vollstadt-Klein *et al*, 2011). Therefore, future fMRI studies should assess in detail whether increased alcohol cue-evoked reactivity is indeed due to enhanced reactivity to alcohol cues, or rather (or additionally) due to reduced reactivity to natural rewards. This could have implications for treatment: rather than attempting to reduce the appeal of alcohol, one could promote the appeal of naturally rewarding stimuli.

A few limitations of the present study need to be mentioned. First, the duration of abstinence of patients varied between 1 week and 6 months, which may have influenced craving and automatic processes. However, length of abstinence was neither negatively correlated with BOLD responses in our ROIs in the approach alcohol contrast, nor with BOLD responses in the dlPFC in the avoid alcohol contrast. Therefore, alcohol approach bias-related brain responses may be independent of abstinence and could hence play a significant role in relapse even after long-term abstinence. Second, there were more smokers in the alcohol-dependent group than in the healthy control group. An exploratory analysis revealed that when including smoking behavior as a covariate, mPFC activity did not reach significance *(p*>.05 FWE). It hence cannot be excluded that the mPFC effects were due to smoking rather than alcohol-dependence or to the combination of both addictive behaviors. This is, however, unlikely since our task was exclusively focused on responses to alcohol and softdrink cues, rather than smoking cues. Moreover, smoking behavior was highly correlated with alcohol use and craving in patients. Consequently, including smoking as a covariate may remove variance explained by drinking behavior. Furthermore, although smoking generally influences BOLD (Jacobsen *et al*, 2002), contrasting approach versus avoid trials made the results independent of general differences in BOLD response due to nicotine use.

In summary, our findings suggest that the automatic alcohol approach bias is related to changes in the motivational system in alcohol-dependent patients. Even when patients express an explicit wish to remain abstinent, reflexive embodied reactions to alcohol and motivational brain mechanisms are likely to make patients vulnerable for relapse. The findings have implications for treatment of alcohol addiction. Treatment generally focuses on the improvement of conscious control (cognitive behavioral therapy or counseling) and reduction of craving by pharmacotherapy. However, our current results and recent clinical effects of bias modification training (Eberl *et al*, 2012; Wiers *et al*, 2011) suggest the automatic drug approach bias as a potential target for clinical intervention. Future studies should focus on whether and how training influences addictive brain states.

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Appendix

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Tables

Table 1 Demographic and clinical data of alcohol-dependent patients and healthy controls

	Alcohol-dependent patients (n = 20, all male)	**Healthy controls** (n = 17, all male)	***P*-value**
Age	44.30 (7.98)	42.12 (8.3)	.422 ns
BMI	23.98 (3.43)	24.44 (2.33)	.637 ns
Years of Education	10.55 (1.15)	11.29 (1.72)	.141 ns
WAIS matrices score	15.21 (4.43)	17.24 (6.13)	.260 ns
STAI-T	36.00 (8.30)	34.24 (12.09)	.630 ns
STAI-S	32.95 (8.20)	32.24 (7.09)	.780 ns
DAQ	14.30 (6.73)	4.88 (4.43)	.000 ***
Lifetime alcohol intake (kG)	2052.74 (2821.01)	153.62 (225.92) [a]	.007 ***
AUDIT	27.05 (7.82)	2.82 (1.67)	.000 ***
ADS	16.43 (8.04) [b]	-	-
Abstinence (days)	53.40 (49.51)	-	-
Number of detoxifications	3.90 (6.72)	-	-
Duration of dependence (years)	16.55 (8.52)	-	-

Abbreviations: BMI, Body-Mass Index; WAIS, Wechsler Adult Intelligence Scale; STAI-T, Trait Anxiety Inventory; STAI-S, State Anxiety Inventory; DAQ, Desire for Alcohol Questionnaire; AUDIT, Alcohol Use Disorders Test; ADS, Alcohol Dependence Scale;
[a] *N*=16; [b] *N*=19; * *p*<.05; ** *p*<.01; *** *p*<.001

Supplementary Table S1. Whole-brain activations: groups effects of approaching alcohol, avoiding alcohol and the correlation of approaching alcohol with subjective craving in alcohol-dependent patients.

Brain region	**Hemisphere**	**Cluster size**	**MNI coordinates of peak activation (*x y z*)**			**T_{max}**
Approach alcohol (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink)						
AD > HC						
Medial prefrontal cortex	L/R	30	0	59	7	4.43 ***
Middle/ Superior temporal gyrus	L	39	-42	-61	22	4.04 *
Middle/ Inferior frontal gyrus	L	12	-48	11	40	3.91 *
Posterior cingulate cortex	R	24	21	-52	25	3.82 *
Posterior cingulate cortex	L	13	-6	-49	22	3.76 *
Superior temporal gyrus	R	10	57	-28	13	3.33 *
Avoid alcohol (avoid alcohol>approach alcohol) > (avoid softdrink>approach softdrink)						
AD > HC						
No suprathreshold voxels						
Correlation DAQ alcohol craving with approach alcohol (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink)						
AD						
Precuneus	L	26	-24	-61	34	5.00 *
Insula/	R	41	39	8	-5	4.49 *
Amygdala			30	-7	-11	4.25 ***
Parahippcoampal gyrus	R	10	15	-31	-14	4.07 *

*** *p*<.05 FEW, SVC
* *p*<.001 uncorrected, k≥10

Figures and legends

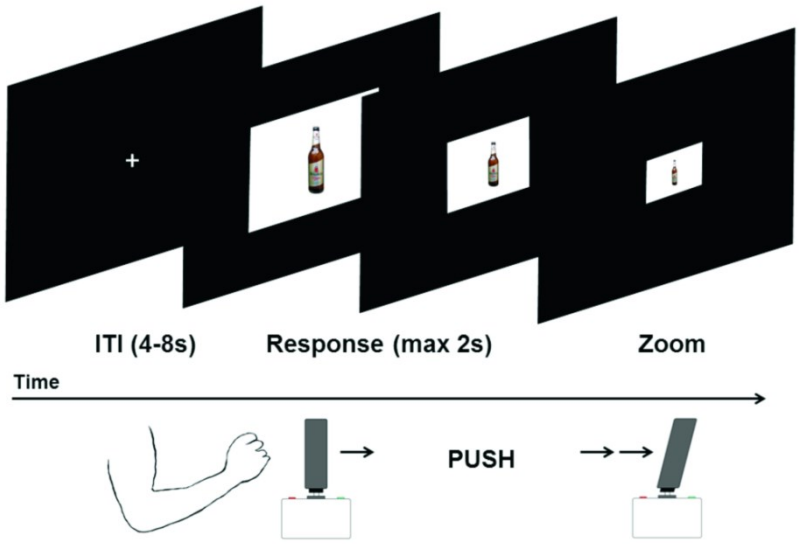

Figure 1 Schematic overview of an avoid alcohol trial on the approach avoidance task (AAT), in which the cue zooms out while pushing on the joystick.

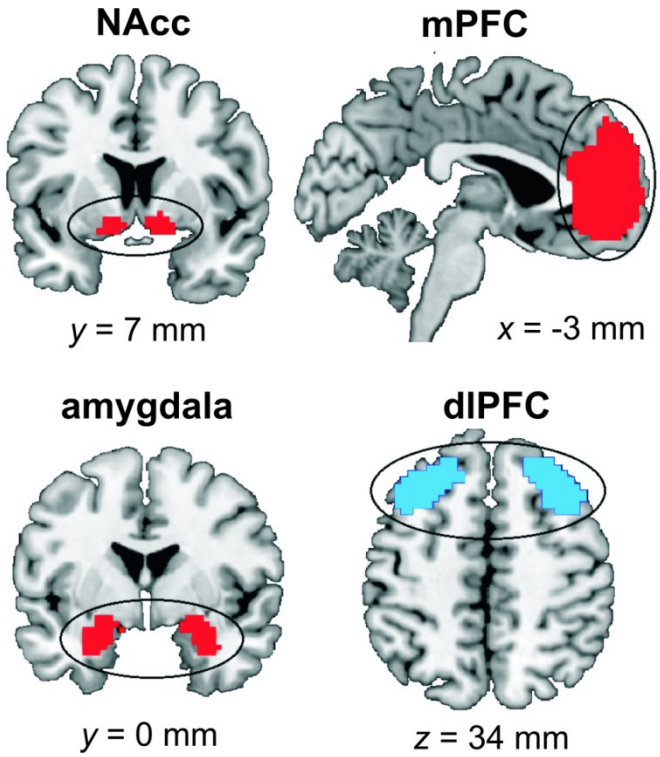

Figure 2 A-priori defined regions of interests of the motivational system (NAcc, mPFC, amygdala) and of the cognitive control system (dlPFC), shown in red and blue respectively.

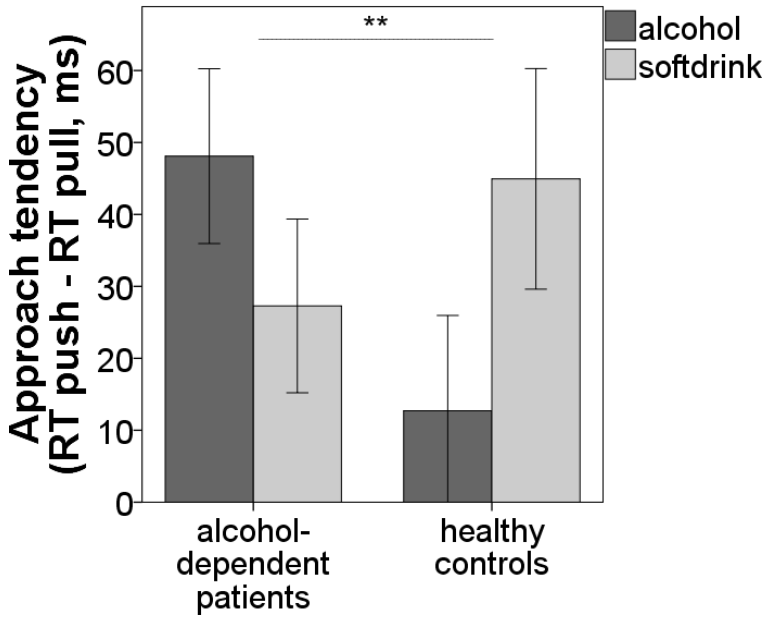

Figure 3 Mean approach tendencies (RT avoid – approach) for alcohol and softdrink cues. There was a significant interaction effect of drink type × group (p<.01), with alcohol cues being approached faster in alcohol-dependent patients as a trend (p<.06). Error bars depict 1 standard error (SE) above and below the mean.

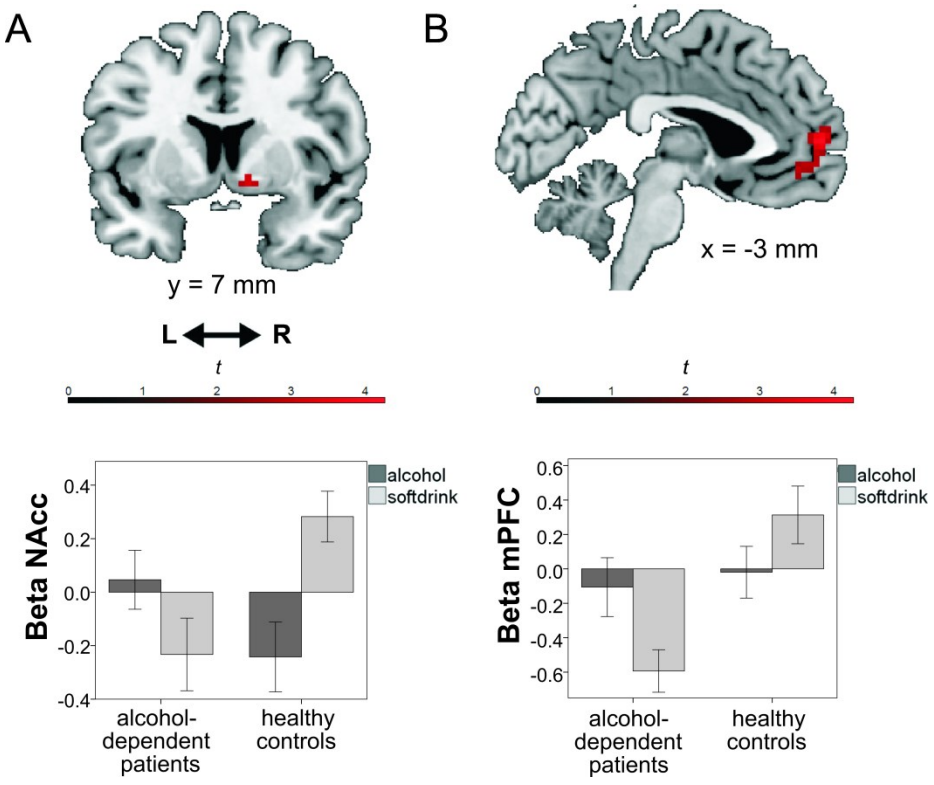

Figure 4 NAcc (A) and mPFC (B) showed higher BOLD response in alcohol-dependent patients compared to healthy controls in the alcohol approach bias contrast (approach alcohol>avoid alcohol) > (approach softdrink>avoid softdrink). The effects were significant at p<.05 (FWE, SVC). For visualization, activations within our NAcc ROI

(panel A) and our mPFC ROI (panel B) are plotted with a threshold of $p<.005$ uncorrected, on a standard anatomical brain template using MRIcron software. Bar plots of mean beta values per stimulus category (alcohol/softdrink) and per group (extracted from all voxels that were active at $p<.005$, uncorrected) are for visualization purposes only.

Since performing post-hoc tests on these extracted betas would be considered double dipping (Kriegeskorte et al, 2010), post-hoc *t*-tests on separate approach tendency contrasts were performed using our a-priori NAcc and mPFC ROIs. These revealed that there were no group differences in approach tendency-related activity for alcohol (approach alcohol>avoid alcohol) ($p>.005$ uncorrected). In contrast, approach tendency-related activity for softdrinks (approach softdrink>avoid softdrink) was larger in healthy controls than alcohol-dependent patients, both in the NAcc ($p<.05$, FWE) and mPFC ($p<.05$, FWE).

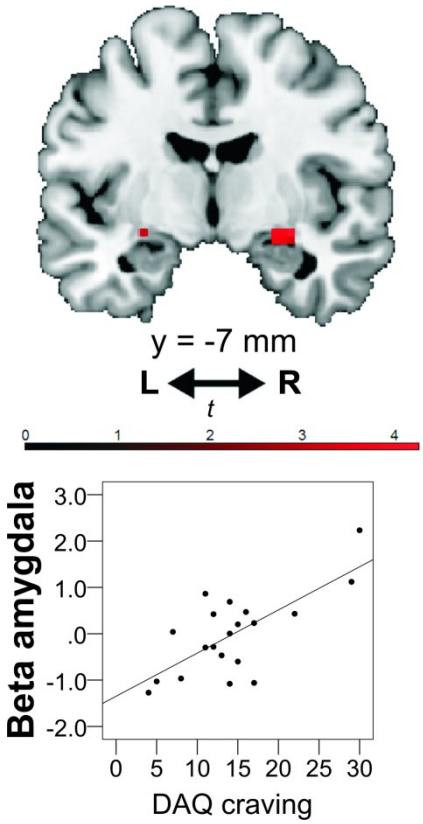

Figure 5 Craving scores correlated positively with alcohol approach bias-related brain activity in the amygdala in alcohol-dependent patients ($p<.05$, FWE, SVC). Activations within the amygdala ROI are plotted here on a standard anatomical brain template using MRIcron software, with a threshold of $p<.005$ uncorrected. Mean beta values were extracted from the activated clusters within the amygdala ROI (at $p<.005$, uncorrected), in order to produce the correlation plot. The correlation plot is for visualization purposes only. No further post-hoc tests were performed on these extracted data since this would be considered double dipping (Kriegeskorte *et al*, 2010).

EXPERIMENT III – EFFECTS OF COGNITIVE BIAS MODIFICATION TRAINING ON NEURAL ALCOHOL CUE REACTIVITY IN ALCOHOL-DEPENDENCE

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Wiers CE, Stelzel C, Gladwin TE, Park SQ, Pawelczack S, Gawron CK, Stuke H, Heinz A, Wiers RW, Rinck M, Lindenmeyer J, Walter H*, Bermpohl F*. Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol-dependence.
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Abstract

Objective In alcohol-dependent patients, the presentation of alcohol cues evokes relatively strong activation in mesolimbic brain areas, such as the nucleus accumbens (NAcc) and amygdala. Moreover, patients show an approach bias for alcohol cues: the behavioral tendency to faster approach than avoid these cues. Cognitive bias modification training (CBM) has the goal to retrain approach biases and has been shown to reduce relapse rates after training. The authors investigated effects of CBM on neural alcohol cue reactivity in detoxified alcohol-dependent patients.

Methods In a double-blind placebo-controlled randomized design, thirty-two abstinent alcohol-dependent patients were assigned to a CBM group or a placebo-training group. Both groups performed an approach avoidance task for 3 weeks, in which the CBM group pushed away 90% of alcohol cues with a joystick, whereas this rate was 50% in the placebo group. Before and after training, alcohol cue-evoked brain activity was measured with functional magnetic resonance imaging.

Results Before training, significant cue-evoked activation was found in the bilateral amygdala, and at trend level in the right NAcc. Activation in both areas correlated with subjective craving scores. After training, the CBM group showed greater reductions in cue-evoked activation in the bilateral amygdala than the placebo group. Decreases in amygdala activity were correlated with decreases in craving within the CBM group but not in the placebo group.

Conclusion These findings provide the first evidence that CBM affects cue-induced mesolimbic brain activity. This reduction of neural cue reactivity may be a key underlying mechanism of the therapeutic effectiveness of CBM.

Introduction

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 due to 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 repeatedly shown in physiological and behavioral studies and is thought to be a key underlying mechanism involved in alcohol craving and inducing relapse, even after years of abstinence (5).

Incentive-sensitization models of addiction suggest fronto-limbic dopaminergic neuroadaptations to underlie the brain physiology of alcohol cue reactivity. Alcohol intake has been shown to directly release dopamine in the ventral tegmental area (VTA), further projecting to mesolimbic structures such as the nucleus accumbens (NAcc) and basolateral amygdala as well as frontal areas (5, 6). Since dopamine signals motivational relevance, it has been hypothesized as a key neurobiological substrate of drug-cue learning. For example, neuroimaging studies show that when alcohol-dependent patients are exposed to alcohol cues, activation in reinforcement-related mesolimbic areas is evoked (5, 7). Activity in these areas has been positively related to craving (8, 9), reward processing (10-13) 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 behavioral and/or pharmacological therapy of only a few weeks may decrease cue-evoked activation in the NAcc (16, 17) and amygdala (18) in alcohol-dependent patients. Thus, training effects on NAcc 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: the tendency to faster approach than avoid these cues on an approach avoidance task (AAT) (9, 19, 20). In this task, participants push and pull pictorial cues with a joystick and patients have been shown to faster pull than 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 AAT has been adapted into a cognitive bias modification training (CBM), in which patients implicitly learnt to avoid alcohol cues. In heavy drinkers, CBM training has been shown to decrease the approach bias and reduce post-training alcohol intake (22). Moreover, in two recent randomized-controlled studies, CBM reduced relapse rates up to 13% in alcohol-dependent patients, compared to a placebo-training group (19) and compared to a non-training group (23). Although this shows the clinical potential of CBM in alcohol-dependence, it is as yet unclear how CBM affects brain function. For instance, CBM could directly reduce the incentive salience of alcohol cues and neural alcohol cue reactivity (2, 24). Understanding the mechanisms underlying CBM can help to further enhance its efficacy and thus further improve treatment of alcohol-dependence.

In the current study, we studied the effects of CBM on neural reactivity evoked by alcohol cues, in alcohol-dependent patients in a double-blind randomized placebo-controlled design. Patients were randomly assigned to a CBM-training group or a placebo-training group, and performed CBM for 3 weeks. The CBM group pushed away 90% of alcohol cues, whereas this rate was 50% in the placebo group. Before and after training, blood-oxygen-level dependence (BOLD) responses to alcohol cues were measured in a Siemens 3 Tesla Magnetic Resonance Imaging (MRI) scanner. We expected, first, enhanced alcohol cue reactivity in the amygdala and NAcc

over all subjects before training. Second, we expected cue reactivity to decrease due to CBM training in amygdala and NAcc. Third, changes in cue reactivity in these regions were expected to covary with changes in craving.

Method

Subjects

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. Thirty-six male alcohol-dependent inpatients 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 dependence (M.I.N.I. plus, an International Neuropsychiatric Interview; 25), being abstinent from alcohol longer 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.

Patients were randomly assigned to a CBM-training group or a placebo-training group. Two patients did not complete the training (1 CBM, 1 placebo) and two patients could not be present at the second day of testing due to administrative reasons (both CBM). The final sample consisted of 15 CBM versus 17 placebo-training participants. Participants completed the Alcohol Dependence Scale to assess the severity of alcoholism (26), the Matrix Reasoning of the Wechsler Adult Intelligence Scale (WAIS) as a proxy for general intelligence (27) and the Spielberger's State-Trait Anxiety Questionnaire (STAI) to evaluate state and trait anxiety (28). Groups did not differ in age, years of education, intelligence scores or clinical variables (Table 1). Smokers were abstinent from tobacco at least 1.5 hours before scanning.

Experimental tasks at pretest and posttest

Approach Avoidance Task

The AAT was used to measure approach bias, before and after training (29). Participants pushed and pulled pictures with a joystick, in response to the format of the cue (landscape or portrait). Participants had to respond to a cue within two seconds and pulling and pushing the joystick increased and decreased the size of the cue respectively. In the task, twenty practice trials were followed by 80 test trials that were presented over two blocks. Picture format to response assignment was counterbalanced and response type assignment did not differ between two groups (χ^2=0.54, p=.46). A set of 40 alcohol and 40 softdrink images was used (9).

fMRI Cue Reactivity

For the fMRI paradigm, the same 80 pictures as in the AAT were presented over eight blocks per stimulus category. Each block consisted of five stimuli, each presented for 4 seconds. To check whether patients were focused on the task, four oddball blocks were added, containing four alcohol or softdrink stimuli and an oddball cue: a picture with 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 five-point Likert scale, and alcohol craving was assessed with the Desire for Alcohol Questionnaire (DAQ) (30).

Cognitive Bias Modification training
The CBM training scheme was an adapted version of the AAT (19, 23). Both groups performed six training sessions over three weeks, each consisting of 400 trials (approximately 15 minutes). The experimental CBM group pushed away alcohol in 90% of the cases and pulled alcohol in 10%, whereas this ratio was 50/50 in the placebo group. Twenty cues were used for training (10 alcohol and 10 softdrink (19, 23)). To test for effects on cue reactivity based on stimulus categories (alcohol versus softdrink) rather than on specific pictures, pictures in the training were different but comparable to cues used in the pre and post-training AAT and fMRI cue reactivity.

fMRI acquisition and preprocessing
Scanning took place in a 3 Tesla whole-body MRI scanner (MAGNETOM Trio, TIM-Technology; Siemens, Erlangen, Germany), equipped with a 12-channel head coil. A standard T2- weighted EPI sequence was used with the following parameters: sequential descending acquisition, repetition time 2s, echo time 25ms, flip angle $\alpha=80^{\circ}$, 64×64 pixels in-plane resolution, 34 slices, slice thickness 3 mm, voxel dimensions $3\times3\times3$ mm^3, a .75mm gap between slides, field of view $192\times192mm^2$ (9). Per session, 141 images were acquired.

Functional data analysis was performed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). During preprocessing, scans were spatially realigned, slice-time corrected and normalized to the standard Montreal Neurological Institute EPI template. Smoothing was performed with an 8mm full width at half-maximum Gaussian kernel. Participants did not move more than 2 mm or 2 degrees within runs.

Statistical analysis
For the AAT, responses that were missed or incorrect and response times (RTs) longer than 3 standard deviations (SDs) above the mean 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 softdrink cues ([alcohol push-pull] – [softdrink push-pull]). Positive alcohol approach bias scores indicate an alcohol approach bias, whereas negative approach bias scores indicate an avoidance bias for alcohol relative to softdrinks. 2×2 mixed ANOVAs on alcohol approach bias scores, DAQ craving scores and picture ratings were calculated, with time (pre- versus post-training) as a within-subject factor and group (CBM versus placebo) as a between-subject factor. Post-hoc group comparisons were performed with two-sided two-sample t-tests and an alpha of .05. Effects with significance levels of $p<.1$ are reported as trends.

Three fMRI regressors were built for every subject: alcohol blocks, softdrink blocks and oddball blocks, each with a duration of 20s. They were convolved with the hemodynamic response function (HRF) with default temporal filtering of 128s. On the single subject level, the following contrasts were calculated (1) alcohol cue reactivity pre training: ([alcohol > softdrink] pre training), (2) alcohol cue reactivity pre-post training: ([alcohol > softdrink] pre training) – [alcohol > softdrink] post training). On the second level, t-tests were used to calculate (1) alcohol cue reactivity pre training in both groups and (2) alcohol cue reactivity pre-post training in CBM

versus placebo-training. Post-hoc t-tests were used using our a-priori ROIs to explore directions of the interaction of time × group.

Based on our hypotheses, bilateral NAcc and amygdala were chosen as regions of interest (5, 9, 14, 31). NAcc and amygdala ROIs were defined using the human anatomical WFU Pickatlas (32). ROIs were used for small-volume correction (SVC) of the results, with a significance threshold of $p<.05$, family wise error-corrected (FWE). Results that were $p<.1$, FWE were reported as a trend. Exploratory whole-brain analyses are presented in supplementary materials.

Behavioral approach bias scores, craving and alcohol picture ratings before training were correlated with BOLD contrast (1) alcohol cue reactivity pre training, using our ROIs. For behavioral variables showing a positive correlation within our ROIs before training, we computed pre-post training difference scores and correlated these with significant activations in (2) alcohol cue reactivity pre-post training.

Results

Behavioral effects of CBM training

Alcohol approach bias scores pre-, post- and pre-post training were distributed normally in both groups (Kolmogorov-Smirnov test: all $p>.62$). Mean error rates were 3.04±3.22%SE before training and 2.65±3.83% after training collapsed over the groups. There were no main effects of group or time and no interaction effect of group × time.

For the alcohol approach bias RT scores, there was no significant interaction effect of group × time ($F_{30}=1.53$, $p=.23$) and no main effects. Exploratory t-tests showed that, although groups did not differ before and after training, RTs decreased as a trend in the CBM-training group (bias pre=11.90±64.01, bias post=-25.53±55.80; $t_{14}=1.18$, $p=.091$), but not in the placebo group (bias pre=-9.35±122.21, bias post=21.50±99.89; $t_{16}=-.64$, $p=.53$).

Subjective alcohol craving and picture ratings

For DAQ craving scores, there was a main effect of time ($F_{30}=9.32$, $p=.005$, $\eta^2=.23$). In both groups, DAQ craving scores were higher before training (mean CBM=15.20±1.79, mean placebo=12.29±1.21) than after (craving CBM=12.33±1.60, craving placebo=10.36±.87). There was no significant interaction effect of group × time for DAQ craving scores ($F_{30=}3.34$, $p=.56$). Exploratory paired t-tests showed that, although groups did not differ before and after training, DAQ craving scores significantly decreased in the CBM group ($t_{14}=3.86$, $p=.002$), but not in the placebo group ($t_{16}=1.47$,$p=.16$).

There was a significant interaction effect of group × time for arousal ratings of alcohol pictures ($F_{30}=4.19$, $p=.05$, $\eta^2=.12$), with arousal ratings decreasing in the CBM group (arousal pre=1.02±.40, arousal post=.88±.51, $t_{14}=2.01$, $p=.064$) but not in the placebo group (arousal pre=.98±.34, arousal post=1.04±.38, $t_{16}=.82$, $p=.43$). There were no significant effects of group × time for valence ratings ($F_{30}=1.90$, $p=.18$). Before and after training, 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 pictures of animals, before and after training.

Before training, subjects pooled over both groups showed alcohol cue-evoked brain activity in the amygdala (peak left MNI [x,y,z]=[-21,-7,-14], t=4.98, p<.001, FWE SVC;peak right=[21,-7,-17], t=2.87, p=.052, FWE SVC) while viewing alcohol cues versus softdrinks. In this contrast, the right NAcc was activated at a trend level (peak=[18,8,-11], t=2.48, p=.057 FWE SVC). See Figure 1 for pre-training activations in amygdala and NAcc. See supplementary data S1 for whole brain activations, showing no relevant between-groups differences before training.

When further assessing group differences in alcohol cue reactivity pre-post training, the CBM-training group showed significantly greater reductions in alcohol cue-evoked activation in the bilateral amygdala (peak left=[-15,-1,-23], t=2.97, p<.05, FWE SVC; peak right=[27,2,-20], t=3.08, p<.05 FWE SVC) compared to the placebo group (see Figure 2). This effect was not present for the NAcc, even at a more liberal threshold of p<.005 uncorrected. After training, CBM had significantly lower activation in the left amygdala than placebo (peak=[-15,-1,-26], t=3.86, p<.05 FWE SVC). See S1 for whole brain activations.

Post-hoc t-tests on pre-post cue reactivity within groups, demonstrated a significant reduction of amygdala activity pre-post training in the CBM group (left amygdala=[-27,2,-17], t=3.58 p<.05, FWE SVC; right=[24,2,-20], t=2.88 p<.05 FWE SVC). However, this was not the case for the placebo group, even at p<.005 uncorrected.

Correlations with behavioral measures

Before training, both groups' DAQ craving scores significantly correlated with alcohol cue-induced amygdala activity (left amygdala=[-18, -7,-17], t=6.15, p<.001 FWE SVC); right=[21,-4,-23], t=3.88, p<.01 FWE SVC) and with the right NAcc at trend level (peak=[15,11,-8], t=2.15, p=.057 FWE SVC). Arousal ratings also correlated with cue reactivity in the bilateral amygdala (left amygdala=[-27,-4,-20], t= 3.67, p<.01 FWE SCV; right=[21,-1,-14], p<.05), and the right NAcc as a trend (peak=[18,8,-11], p=.052). Approach bias and valence ratings did not correlate with alcohol cue-induced activations in our ROIs.

In the CBM group, the difference of pre-post amygdala activity correlated positively with the decrease in DAQ alcohol craving (left amygdala=[-15,-4,-20], t=3.09, p<.05, FWE SVC; right=[24,2,-20], t=2.71, p=.1, FWE SVC). This was not the case for the placebo group. Moreover, when comparing the two groups with respect to the correlation slopes of pre-post cue reactivity and pre-post craving, there was an effect in the right amygdala (peak=[30,2,-17], t=3.85, p<.01, FWE SVC), providing stronger evidence for a greater correlation in the CBM group. See Figure 3 for the regression slopes of pre-post alcohol craving and amygdala activity in both groups. There were no significant correlations between decreases in arousal ratings and decreases in amygdala activations.

Discussion

The current study aimed at studying the effects of cognitive bias modification training on neural alcohol cue reactivity. The results provide first evidence that CBM can affect cue-induced amygdala activity, an area previously associated with alcohol cue reactivity, craving and relapse prediction (5, 7, 8, 9, 12, 14, 17). Before training, both groups showed alcohol cue reactivity in the amygdala and, at trend level, the NAcc, which correlated positively with craving scores and arousal ratings of alcohol cues. These findings replicate previous studies in alcohol dependence and may indicate the severity of dependence (5, 7, 8, 9, 12, 33). When comparing pre- with post-

training alcohol cue-evoked brain reactivity, amygdala activity differed between the two groups: while amygdala activity decreased in the CBM group, this effect was not shown for the placebo group. Moreover, the decrease in amygdala activity correlated with a decrease in alcohol craving scores in the CBM group, but not in the placebo group. Therefore, reduction of alcohol cue-induced amygdala activity may be an important underlying mechanism contributing to the previously found therapeutic effectiveness of CBM (19, 23) and may serve as a biomarker for reductions in levels of 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 the amygdala has been described as the processing of the personal motivational salience of stimuli (35). In drug-dependent patients, the area has been associated with craving while passively viewing drug cues (12, 36), when approaching versus avoiding alcohol cues on the AAT (9) and when smelling alcohol in alcohol-dependence (18). Schneider et al (18) showed that the combination of pharmacological and behavioral therapy reduced amygdala activity in alcohol-dependent patients, whereas a healthy control group did not show reductions in amygdala activation over the same period of time. Although Schneider et al (18) could not distinguish whether the effect was due to behavioral or pharmacological interventions, it did show that the amygdala can be flexibly modulated over time with respect to alcohol-induced cue reactivity. Moreover, it has recently been shown that emotional cue-evoked amygdala activity can be modulated by attentional CBM in anxious individuals (37). A possible interpretation of the current results, in which CBM reduced amygdala cue reactivity, is that CBM reduces the motivational salience of alcohol cues. In line with this interpretation, we found that CBM reduced arousal ratings of alcohol cues. Moreover, CBM-induced reductions in amygdala activation correlated with reductions in alcohol craving.

How then could CBM cause such a reduction in salience? It may be that this effect is related to recent 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 CBM (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. Future studies are needed to provide evidence for or against the hypothesis that the mediating mechanism of CBM involves, at least partially, reductions in the salience of alcohol cues.

Despite significant effects of CBM on neural cue reactivity, its correlation with craving and behavioral effects on arousal ratings, we could not replicate the interaction effect of group × time on approach bias scores found by Eberl et al. (23) and Wiers et al. (19, 22). Since effects of CBM on approach bias and alcohol craving are in the hypothesized direction (we found a reduction in approach bias by trend as well as a significant reduction in craving in CBM, but not in the placebo group) it is likely that the lack of effect could be explained by the relatively small sample size in this study. Although behavioral effects of training have been found in sample sizes of 300 to 600 (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 the cues 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 CBM training generalize to other, non-trained stimuli, at least in terms of neural effects and in arousal ratings. Further, we scanned patients after at least one month of abstinence, which may have reduced the likelihood of detecting effects of training on behavior and brain activation. This may explain the weak initial activation of NAcc before training and that we did not observe hypothesized reductions in the NAcc between groups. Another limitation is that the current intervention study assessed cue reactivity but did not additionally measure neural activity related to alcohol approach/avoidance tendencies. In a recent study, NAcc and amygdala were found to be related to the alcohol approach bias (9). Future studies are needed that focus on effects of CBM in an approach/avoidance context, rather than passive viewing, and their relation to alcohol craving and relapse.

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

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Figures and Legends

Table 1. Clinical data of participants in the CBM- and Placebo-training group			
Characteristic	**CBM-training group** Mean (SD)	**Placebo-training group** Mean (SD)	**p-value**
Age, years	45.33 (6.84)	42.88 (8.31)	.37
Years of education	10.60 (1.45)	10.47 (1.33)	.79
WAIS intelligence	15.57 (5.20) [a]	14.06 (5.09)	.42
Length of abstinence, days	36.87 (27.01)	57.35 (39.87)	.10
Duration of dependence, years	17.53 (9.74)	13.06 (6.88) (range 2-30)	.14
Number of detoxifications	5.87 (8.59) (range 0-26)	3.59 (7.20) (range 0-30)	.42
Alcohol intake before admission, grams/day	332.55 (213.65)	244.15 (164.19)	.20
ADS score Alcohol Dependence Scale score (ADS; 26)	17.87 (9.63)	14.50 (5.45)	.24
Number of smokers	12 (80%)	15 (88%)	.52 [b]
STAI trait	35.21 (8.42)	34.47 (7.42)	.80
STAI state	32.67 (8.10)	33.82 (8.02)	.69

Abbreviations: ADS: Alcohol Dependence Scale**,** STAI: Spielberger's State-Trait Anxiety Questionnaire, WAIS: Wechsler Adult Intelligence Scale
[a] n = 14 [b] Chi-squared test

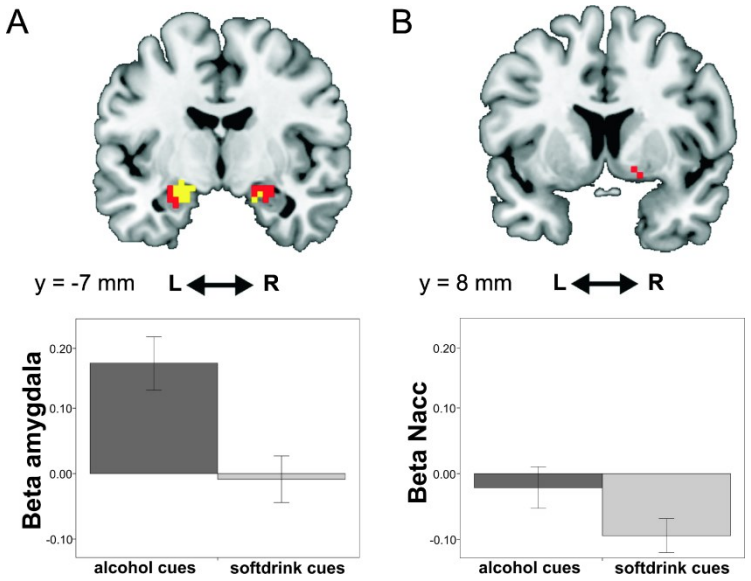

Figure 1. Before training, both groups of alcohol-dependent patients showed significant alcohol cue reactivity (alcohol-softdrink) in the bilateral amygdala (p<.05 FWE SVC; panel A), and trend-wise in the right nucleus accumbens (p=.057 FWE SVC; panel B). Error bars depict 1 SE of the mean. For graphical purposes, significance levels of p=.05 (red) and p=.005 (yellow) uncorrected were used to plot activations. Activations in both areas correlated with alcohol craving scores and arousal ratings of alcohol cues.

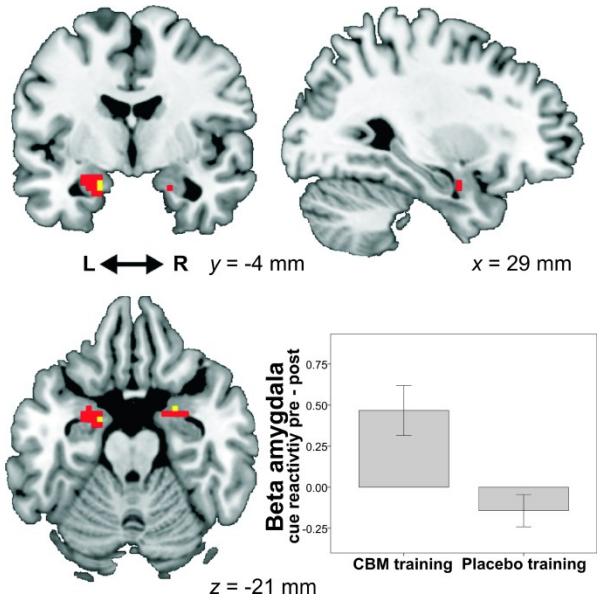

Figure 2. Change of pre-post cue reactivity (alcohol-softdrink) in the CBM group compared to the placebo training group. While the bilateral amygdala activation was reduced in the CBM trainings group (p<.05 FWE SVC), there was no reduction in the placebo trainings group, not even at p<.005 uncorrected. Error bars depict 1 SE of the mean. For graphical purposes, significance levels of p=.05 (red) and p=.005 (yellow) uncorrected were used to plot activations

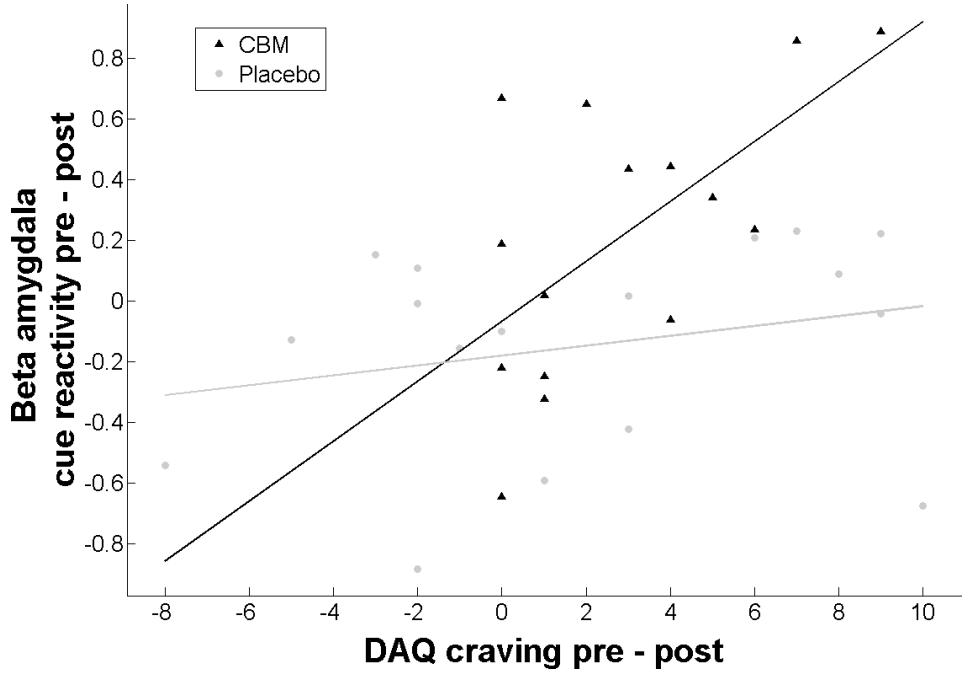

Figure 3. Correlation of the pre-post training change in amygdala cue reactivity (alcohol-softdrink) with DAQ scores in CBM and placebo training group. In the CBM group (black triangles), the difference of pre-post amygdala activations correlated significantly with the decrease in DAQ alcohol craving, whereas this was not the case for the placebo training group (gray dots), not even at p<.005 uncorrected. Beta values of activations within the amygdala ROI were extracted per subject at p=.005 uncorrected.

Supplementary Materials

Table S1. Relevant alcohol cue reactivity (alcohol > softdrink) contrasts, before training, pre-post training, and after training

Brain region	Hemisphere	Cluster size	MNI coordinates of peak activation (x y z)			T_{max}
Pre training, both groups						
Orbitofrontal cortex	L	230	-45	29	-14	5.14 *
Amygdala/ Hippocampus	L	62	-21	-7	-14	4.98 ***
Orbitofrontal cortex	R	41	33	35	-14	4.83 *
Superior parietal lobule	L	22	-24	-58	46	4.30 *
Inferior occipital gyrus	R	107	45	-79	-8	4.25 *
Inferior temporal lobe	L	25	-45	-46	-17	3.98 *
Middle frontal gyrus/ Insula	L	139	-36	14	40	3.92 *
Superior parietal lobe	R	55	27	-58	49	3.81 *
Insula	R	34	27	17	-20	3.81 *
Supplementary motor area	L/R	69	0	26	61	3.63*
Middle temporal gyrus	L	15	-66	-16	-14	3.32 *
Inferior frontal gyrus	R	20	45	5	34	3.32 *
Hippocampus/Amygdala/Putamen	R	16	21	-13	-20	3.27 *
Inferior frontal gyrus	R	11	45	26	10	3.26 *
Superior temporal gyrus	L	10	-33	14	-38	3.05 *
Middle Occipital Gyrus	L	10	-45	-76	-8	2.97 *
Pre training, CBM > placebo						
Superior Frontal Gyrus	R	34	18	59	16	3.12 *
Pre training, placebo > CBM						
No suprathreshold voxels						
Pre-post training, CBM > placebo						
Cerebellum	R	34	15	-28	-26	3.78 *
Amygdala	L	11	-15	-4	-20	3.47 ***
Superior Temporal Gyrus	R	16	42	11	-26	3.35 *
Caudate	R	24	3	14	1	3.12 *
Cerebellum	L	10	-12	-31	-20	3.10 *
Post training, placebo > CBM						
Amygdala/Para-hippocampus	L	14	-15	-1	-26	3.86 ***

*** $p < .05$ FWE SVC

* $p < .005$ uncorrected, $k \geq 10$

B DSM criteria for nicotine and alcohol dependence

- DSM-IV criteria for Nicotine Dependence

The user must demonstrate at least three of the following criteria occurring at the same time during a 12-month period:

1. Tolerance - Signs of tolerance are a need for a markedly increased amount of nicotine to produce the desired effect or a diminished effect with continued use of the same amount of nicotine.
2. Withdrawal, as manifested by either the characteristic nicotine withdrawal syndrome, or nicotine (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.
3. Nicotine is used in larger amounts or over a longer period than intended.
4. The user has a persistent desire or makes unsuccessful attempts to cut down on tobacco.
5. Important social, occupational, or recreational activities are reduced because of tobacco use.
6. Use of the substance continues despite recurrent physical or psychological problems caused or exacerbated by tobacco—for example, continuing to smoke despite diagnoses such as hypertension, heart disease, cancer, bronchitis, and chronic obstructive lung disease.

- DSM-IV criteria for Alcohol Dependence

A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following seven criteria, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    b. Markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal, as defined by either of the following:
    a. The characteristic withdrawal syndrome for alcohol (refer to DSM-IV for further details).
    b. Alcohol is taken to relieve or avoid withdrawal symptoms.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or there are unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Source: American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM-IV). Washington, D.C.: APA.

C Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe;

dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze; und

dass ich die zugrunde liegende Promotionsordnung vom 02.12.2008 kenne.

Berlin, August 2013,

Corinde Wiers

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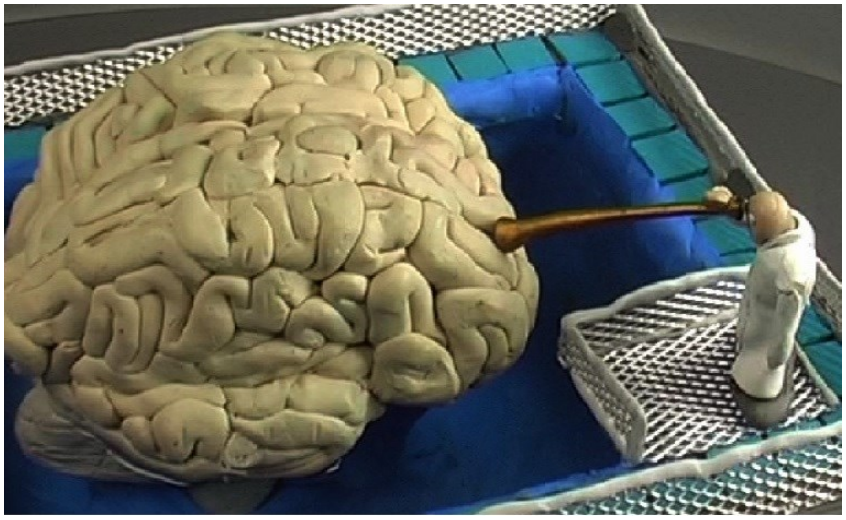
August, 2013



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