Attention for alcohol : on the changeability of appetitive motivational processes in alcohol abuse

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Tim Michaël Schoenmakers

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General Introduction

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This thesis is about changing implicit processes that are related to substance abuse. These implicit processes are hypothesized to be part of the appetitive motivational system. That is, they influence appetitive motivation: the drive to approach and pursue appetitive substances such as drugs and alcohol. In contrast to explicit beliefs about substance use, implicit appetitive processes are not always accessible to peoples' awareness, may operate automatically, and are therefore difficult to control. Central to this thesis is the implicit process 'attentional bias', defined plainly as excessive selective attention for substance-related cues.

The two main goals of this thesis were to understand how alcohol consumption influences appetitive motivational processes, and how implicit appetitive processes influence the motivation to consume alcohol. These questions were addressed by four experimental studies reported in the thesis. The first empirical chapters focus on alcohol prime effects: the direct influence of alcohol consumption on factors of the appetitive motivational system (attentional bias, approach bias, and craving). The final two empirical chapters describe studies on the clinical usefulness of a training method to change attentional bias for alcohol-related cues, i.e. attentional re-training.

The general introduction of the thesis starts with the theoretical background on attentional bias and describes measures of attentional bias. After that, I will discuss findings on consequences of attentional bias and its relation to craving for a substance, substance use and abuse. The final part of the introduction addresses scientific publications on alcohol prime effects and attentional (re-)training that were available when we started designing the empirical studies for my PhD. An up-to-date review on attentional (re-)training studies is given in the general discussion (Chapter 6).

Theoretical background

Early addiction theories have mainly focused on explicit cognitions. Explicit cognitions are reports of feelings or thoughts, such as subjective beliefs about causes and reasons why one

uses an addictive substance[1], mainly measured with questionnaires. A sole focus on explicit cognitions leads to, and partly arrives from the assumption that addictive behaviour is a choice or at least the outcome of rational decision making: weighing the pro's and cons of substance use. In the last decades, however, a number of addiction theories have explained addiction as resulting from both explicit and implicit cognitive processes (see Wiers & Stacy, 2006 for an overview). Implicit processes are not rational but rather automatic, impulsive responses to substance-related cues. As an addiction develops, substance use becomes more automatic and less influenced by elaborated decisions. Here, I will focus on theories that prevail in research on appetitive motivation, implicit processes and attentional bias in specific.

Tiffany (1990) proposed that drug abuse in addicts is largely an automatic, uncontrolled process or 'skill', accomplished by repeated practice. Such automatic, effortless processes are stimulus-bound. This means that substance-related cues (stimuli) - that one attends to - evoke the automatic processes that mediate drug pursuit. Only when drug use becomes hindered, for example when there are no drugs available, this process comes into awareness and subjective urge or craving[2] for the drug is felt. Otherwise, one will pursuit and use his substance without craving for it.

Other theories also endorse the idea that appetitive motivation, i.e. the motivational processes underlying substance use, is not essentially a rational process. The Incentive Sensitization Theory (Robinson & Berridge, 1993) describes how appetitive motivational processes develop and become automatic, stimulus-bound. When one first starts using an addictive substance, the reward system in the brain is activated by the pleasurable effects of the substance, mediated by dopamine release. This leads to 'liking' for the substance. Through classical (Pavlovian) learning, cues (e.g. objects, words, acts, events or places)

[1] In this introduction, 'substance' means any kind of addictive substance, such as alcohol, tobacco, cannabis or any kind of illicit drugs. When necessary, for example when a theory or research finding is limited to one particular substance, this substance will be specified.

[2] Craving has been found to consist of multiple components. Where needed, its components will be specified. However, for the purpose of clarity, I use the term craving for the general desire for a substance, or intensive 'wanting' of the substance.

that are related to substance use become associated with the pleasurable outcome of the substance. Finally, the theory proposes that as a result of repeated substance use, neuro-adaptations in the brain render substance related stimuli highly salient: repeated use leads to the attribution of incentive salience to those stimuli. This means that cues that are often paired with substance use become attractive, 'wanted', notable and eye-catching. Thus cues with incentive salience 'grab' the attention, and are attended to longer than cues without incentive salience, i.e. attentional bias.

'Wanting' in quotation marks refers to the underlying psychological process that controls drug pursuit; since substance-related cues trigger 'wanting' for the substance, the process of appetitive motivation, i.e. drug seeking and use, is initiated when one attends to these cues. The attribution of incentive salience is hypothesized to be automatic and unconscious. As a result, salience attribution - which leads to the manifestation of attentional bias - might produce substance-seeking without the conscious awareness of wanting (Robinson & Berridge, 2000). Thus attentional bias might not in all circumstances go together with self-reported craving. When someone does become aware of 'wanting', he or she will desire or crave the substance, which is equal to wanting the substance in the common sense of the word (*wanting* without quotation marks). Thus the psychological process that underlies drug pursuit might be relatively automatic, without a conscious desire. However, when the process is hindered (e.g. no available drugs; cf. Tiffany, 1990), it will become conscious, leading to self-reported craving.

A typical issue of the Incentive Sensitization Theory is that while substance 'wanting' increases by repeated substance use, 'liking' of the substance remains the same or even reduces concurrently. Thus compulsive substance-seeking and use is mainly steered by substance 'wanting' because the pleasurable drug effects are not stronger than in the beginning and might even be absent (tolerance).

To recapitulate, the incentive sensitization theory explains that substance-related cues can trigger strong 'wanting' because of neuro-adaptations, i.e. changes in the reward centre of the brain. Repeated substance use increases the intensity of incentive salience, i.e. incentive sensitization. Excessive substance use permanently changes the neuropsychological system that is responsible for dopamine transmission (the

neurotransmitter that mediates the reward system). The change in the neural reward system renders the brain permanently, or for a long time, hypersensitive for substance-related cues. This long-lasting hypersensitivity for substance-related cues has been used to explain why addicts are still prone to relapse after a long period of abstinence (also see Kalivas & Volkow, 2005).

Evidence for incentive sensitization comes from studies that found greater activation of reward-circuitries in the brain during exposure to drug-related cues in alcohol abusers than controls (e.g. Tapert et al., 2003; for a review see Wilson, Sayette, & Fiez, 2004). A few studies have provided evidence for automatic processing of substance-related stimuli in addicts. By subliminal presentation of substance-related cues, those studies demonstrated a relation between craving and non-conscious processing of these cues (Ingjaldsson, Thayer, & Laberg, 2003a, 2003b; Rosse et al., 1997). Carter and Tiffany (1999) performed a meta-analysis on studies on cue-induced subjective craving in addicts, with supraliminal cue presentations. They found that the effect size was rather large for smokers, cocaine and heroin addicts, and medium for alcoholics. Another way to examine effects of cue-exposure is measuring inhibition of startle reflexes during exposure. The inhibition of an eyeblink response to a startling noise when confronted with alcohol-related cues indicates the appetitive valence of these cues (Mucha, Geier, Stuhlinger, & Mundle, 2000). Grüsser et al. (2002) found such effects in abstinent alcoholics who verbally reported to have no craving. This indicates that abstinent alcoholics might not recognize their craving or deny their craving, while they do show automatic appetitive responses to alcohol cues. An alternative explanation is that low perceived substance use opportunity, as in a treatment centre, reduces cue induced craving (Wilson et al., 2004), while more automatic processes are still being instigated by exposure to substance-related cues.

Kavanagh, Andrade and May (2005) suggest that substance-related cues automatically evoke intrusive thoughts about that substance. Subsequently, an addictive person starts ruminating about the substance which leads to strong desire for the substance. While these authors recognize that salience of cues does have a function in substance abuse, their focus is on craving as the main motivational force.

In contrast to Tiffany (1990), Cox and Klinger (1988, 2004) regard drinking alcohol as a decisional, volitional act (although it may be *perceived* as outside one's control). Whereas current concerns implicitly bias cognitive processing toward concern-related stimuli, this biased processing does not instigate behaviour by itself. A current concern that is alcohol-related further biases the processing of alcohol-related stimuli. A non-alcohol-related concern biases the processing of other goal-relevant stimuli, preventing alcohol pursuit. Attentional bias for alcohol brings distal determinants of drinking, such as positive expectations and conditioned incentive responses implicitly into focus. Consequently, in the decision to drink or not, these distal determinants gain a proportionally large influence. However, more proximal determinants, such as the presence of alcohol or anxiety provoking situations, determine whether these implicitly activated distal determinants lead to drinking or not.

Finally, Wiers and colleagues (Wiers, Bartholow et al., 2007) focus on the regulation of addictive behaviour. They state that when starting using alcohol, people are still able to regulate appetitive motivational tendencies that are triggered by alcohol-related cues. However, most adolescents are not motivated to regulate them. When alcohol use turns into alcohol abuse, the ability to regulate or control these compulsive tendencies weakens, because alcohol affects those parts of the brain that are responsible for self-regulation.

Taken together, the above mentioned theories all suggest that addiction is partly determined by relatively automatic cue-induced processes that develop over time during substance use. Further, they acknowledge the role of attending to substance-related cues as a consequence *and* predictor of substance abuse. An important goal of the research in this thesis is to investigate the causal role of attentional bias by testing the effect of decreases in attentional bias on addictive behaviour and appetitive motivation. At the same time, this research provides information about the possible clinical usefulness of targeting attentional bias in the treatment and prevention of substance abuse.

Attentional bias: measures & components

In addiction research, different measures of attentional bias have been used. These are reaction time tasks in which participants have to react as quickly as possible to trials in the tasks, thereby indirectly providing information about the magnitude of their attentional bias. Different tasks are capable of measuring different components or types of attentional bias. These types relate to the time-course of attention shifts, e.g. the facilitated or speeded detection of substance-related stimuli, the maintenance of attention, the difficulty to disengage attention or delayed disengagement. I will start with describing an attentional bias task that does not differentiate between these components, but is probably affected by one or more of these components, namely the addiction Stroop task.

Interference task – the addiction Stroop task

The first studies on attentional bias in alcohol have used the emotional Stroop task or addiction Stroop task (Williams, Mathews, & MacLeod, 1996). In this task, substance-related words are presented in different colours in different trials. In each trial, participants have to name the colour in which the word is presented as quickly as possible. The semantic meaning of the word interferes with the cognitive processing of the colour, leading to a relatively slow response. When a word is meaningless or neutral, it is easier to name the colour. The difference in reaction time between neutral and substance-related words (the Stroop effect) is the index for attentional bias. Attentional bias with the Stroop task has been found to be greater in heavy social drinkers than in light social drinkers[3] (e.g. Bruce &

[3] Heavy drinkers are sometimes also referred to as problematic or hazardous drinkers. Social drinkers are people who mainly drink on social occasions. In most research on social drinkers, light drinking males are distinguished as those drinking up to 20 standard units per week (females 14) and heavy drinking males as drinking more than 20 glasses per week (females 14). Hazardous drinking is defined by the World Health Organization as "...a pattern of alcohol consumption that increases the risk of harmful consequences for the user or others." (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001, p. 5). It is indicated by a score of eight or higher on the Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993).

Jones, 2004), in abstinent alcoholics than in social drinkers (e.g. Sharma, Albery, & Cook, 2001; Stetter, Ackermann, Bizer, Straube, & Mann, 1995), in smokers than in non-smokers (e.g. Munafo, Mogg, Roberts, Bradley, & Murphy, 2003), in cocaine addicts than in non-consuming control participants (Hester, Dixon, & Garavan, 2006), and in heroin addicts than in non-consuming controls (Franken, Kroon, Wiers, & Jansen, 2000).

The problem with the interpretation of Stroop task findings is that it is not clear why this interference occurs and what happens with the focusing of attention. According to Posner and Petersen (1990) the attentional system consists of three components: (1) shifting of attention, (2) engagement of attention, thus capturing an object, i.e. focusing, and (3) disengagement of attention, meaning focusing away from the object one was attending to. The addiction Stroop task does not distinguish between biased shifting, biased engagement or biased disengagement. One explanation of Stroop findings is that both the colour and the semantic meaning of the word attract attention. The semantic meaning causes the participant to ruminate, which costs cognitive capacity that interferes with the capacity needed to name the colour of the word. Another explanation is that by network activation, the semantic meaning might automatically attract attention, causing attention to be distracted from the colour of the word. A third explanation has to do with response selection; a participant might tend to name the word instead of the colour (Cohen, Dunbar, & McClelland, 1990; Williams et al., 1996). A final explanation is that someone is first attracted toward the word but then tries to avoid it, causing interference (De Ruiter & Brosschot, 1994). For example, recovered alcoholics might try to avoid alcohol-related stimuli and divert their attention away from the words.

One of the addiction-Stroop interpretations might be true in all cases, but they might also differ between different kinds of users. For example, there is no reason for social users to avoid substance-related stimuli, while alcohol dependent patients might be motivated and able to avoid alcohol-related stimuli in this task. Thus, a Stroop effect should be interpreted as indicating no more than biased processing of substance-related stimuli.

Spatial attention tasks – the visual-probe task

A task that is able to differentiate between different kinds of attentional bias is the visual-probe task (MacLeod, Mathews, & Tata, 1986). In each trial of the visual-probe task, a neutral and substance-related stimulus (words or pictures) are simultaneously presented on a computer screen. After a short presentation time the stimuli disappear and a probe (e.g. a dot) is presented at the spatial location of one of the stimuli. The idea is that the probe is quicker detected at the location where the participant had his/her eyes focused. Thus someone with an attentional bias for alcohol will have detected the probe quicker on trials where it replaced alcohol-related stimuli than neutral. When someone avoids substance-related stimuli, the response latency for neutral words will be faster, since then the attention at stimulus offset was focused away from the substance-related stimuli, but rather on the neutral stimulus. The difference between detection latencies for alcohol and neutral is the index for attentional bias, either attending (speeded detection, difficulty to disengage, maintenance) or avoidance.

By using different stimulus presentation times, the visual-probe task can differentiate between early attention processes and later, slower processes. Since the task measures the locus of attention at the moment the stimuli disappear, a short stimulus presentation duration reflects early attentional processing. This might be called facilitated or engagement of attention or speeded detection of substance-related stimuli. Usually, a presentation duration of less than 200 milliseconds is used, since within 200 ms only one eye movement can be made, so only the first gaze direction is measured.

At longer stimulus presentation durations (commonly between 500 and 2000 ms), one can make more than one eye movement and thus the difficulty to disengage attention or attentional maintenance is measured. Field, Mogg, Zetteler, and Bradley (2004) found that heavy drinkers show a difficulty to disengage (500 ms) and maintenance (2,000 ms), but no early engagement (200 ms) compared to light drinking controls. Noel et al. (2006) found early engagement (50 ms) in alcoholic patients, but not in control social drinkers. Recently, Townshend and Duka (2007) found attentional disengagement or avoidance (500 ms) in alcoholic patients compared to healthy controls. However, Noel et al. (2006) did not find attentional avoidance in alcoholic patients at 500ms. In methadone-

maintained heroin addicts, attentional bias (i.e. attending) was found at 500 ms (Lubman, Peters, Mogg, Bradley, & Deakin, 2000).

To clearly distinguish between different components of spatial attention, one could also measure eye movements during a visual-probe task. This offers an unambiguous measure of attention compared to the measurement of response latencies. Response latencies provide an indirect measure of attention and they inform about the allocation of attention at the time of stimulus offset. In contrast, eye movements are direct manifestations of attention, and the monitoring of eye movements offers the possibility of assessing attention during the entire length of the stimulus presentation. Attentional bias in eye movements, e.g. prolonged maintenance of gaze ('dwell time') or a higher proportion of initial eye movements directed toward substance-related versus neutral cues, has been demonstrated in tobacco smokers (Field, Mogg, & Bradley, 2004b; Mogg, Bradley, Field, & De Houwer, 2003) and cannabis users (Field, Eastwood, Bradley, & Mogg, 2006). However, there has been no research that explored attentional bias in eye movements to alcohol-related cues among heavy drinkers or alcoholics. Chapter 2 describes a study in which we measured eye movements in heavy drinkers.

Spatial attention tasks – Posner exogenous cueing task

Another task that measures the spatial location of attention is the Posner exogenous cueing task (e.g. Posner, Walker, Friedrich, & Cohen, 1984). This is also a spatial attention task like the visual-probe task. A difference is that there is only one stimulus presented at a time. The addiction version of the task starts with a central fixation sign. Then a neutral or substance-related stimulus is presented shortly, either left or right from the screen centre, immediately followed by target left or right from the screen centre. In a valid trial, the target replaces the stimulus. In an invalid trial, the target appears at the other side of the screen than the stimulus. By using a relatively long stimulus presentation (e.g. 500ms), one can test maintenance of attention or avoidance of attention from substance-related stimuli. That is, when subjects are faster in responding to valid substance trials than invalid substance trials or valid neutral trials, this is an indication of attentional maintenance. When subjects are faster in responding to invalid trials than valid trials, this is an indication

of attentional avoidance. That was what Stormark, Field, Hugdahl, and Horowitz (1997) found in abstinent alcoholics compared to social drinkers. At the short interval alcoholics showed slower reaction times at invalidly cued trials, indicating a delayed disengagement from alcohol-related stimuli at 100 ms. Contrary to what is sometimes implied (e.g. Noël et al., 2006, p 1872), this task cannot measure the biased engagement (i.e. speeded detection) of attention since there is always only one cue, left or right from the fixation, and this cue will always attract attention, no matter what kind of cue, neutral or substance-related.

Spatial attention tasks – Flicker paradigm

Finally, a task that also measures the spatial attention processes is the Flicker Paradigm to induce change blindness (Simons & Levin, 1997). In this task a composition of substance-related and neutral stimuli is presented, each category on one side of the composition. This visual display is presented shortly and then changes to another display that is similar to the first, with one object (substance or neutral) changed. The computer changes these displays back and forward ('flickering') until the participant detects the change. When the substance-related change is detected faster than the neutral change, this is an indication of attentional bias. The Flicker task is rather slow; it usually takes a few seconds to detect a change. Also, there are multiple substance-related stimuli in the task that can attract attention, but only one changes. Therefore, the task cannot measure speeded detection of substance-related stimuli. Faster substance-related change detection than neutral change detection likely reflects a continued attentional focus toward substance-related stimuli (Yaxley & Zwaan, 2005), possibly related to the maintenance of attention as measured by the visual-probe task with a long stimulus presentation duration.

The advantage of the Flicker task is that it is more ecologically valid, because it presents multiple stimuli in stead of just one or two. It is also unique in that one needs only one trial instead of many to measure attentional bias. This, however, is also a disadvantage when one is interested in individual attentional bias scores; it is probable more valid in measuring group means. Jones and colleagues (B. T. Jones, Jones, Smith, & Copley, 2003; see also B. C. Jones, Jones, Blundell, & Bruce, 2002) found faster substance-related changes and slower neutral related changes in heavier versus lighter users of alcohol and cannabis.

Another study found that smokers, but not non-smokers who were unaware of the goal of the experiment, were faster to detect a smoking-related than non-smoking related change (Yaxley & Zwaan, 2005).

Summary of attentional bias findings for alcohol

Altogether, an abundance of research shows that heavy social drinkers and alcoholics show attentional bias. Stroop tasks show that there is cognitive interference of alcohol-related stimuli in both heavy drinkers and abstinent alcoholics. Further, it seems likely that heavy social drinkers mainly show maintenance of attention to alcohol-related cues once they have detected an alcohol stimulus, but they do not show an automated rapid shift of attention toward alcohol-related cues. Alcoholics in treatment have been shown an early detection in one study (Noël et al., 2006) and a difficulty to disengage from those stimuli at short stimulus presentation time (Stormark et al., 1997). Additionally, findings in slower attention processes in alcoholic patients have been inconsistent: avoidance in two studies (Stormark et al., 1997; Townshend & Duka, 2007), but also no attentional maintenance in another study (Noël et al., 2006). Possibly, some alcoholic patients are able to avoid these stimuli, whereas others are not, leading to an overall average of zero (Noël et al., 2006) or a negative overall bias (Townshend & Duka, 2007). This might explain why some alcoholics relapse and others do not (cf. Cox, Hogan, Kristian, & Race, 2002). For reviews on attentional bias findings see also Cox, Fadardi, and Pothos (2006), Field and Cox (2008), Field, Mogg, and Bradley (2006), Franken (2003), and Robbins and Ehrman (2004).

Is attentional bias causally related to addiction?

Attentional bias is assumed to have causal effects on substance abuse, addiction development and maintenance (Franken, 2003; Weinstein & Cox, 2006). In empirical research reports, it has been found to correlate with craving, alcohol use, relapse, and severity of the addiction. However, there is little evidence from experimental research demonstrating that attentional bias *leads* to addictive behaviours. It might thus be that attentional bias is merely an epiphenomenon of addiction, not a causal agent. Here, I will

discuss empirical studies on the (causal) relation between attentional bias and other variables associated with addiction.

Craving

A relationship between craving and attentional bias is not always found. Although there is empirical evidence for the relation between craving and attentional bias in addictive patients (e.g. Franken, Kroon, & Hendriks, 2000; Franken, Kroon, Wiers et al., 2000; Sayette et al., 1994), and heavy alcohol drinkers (Field, Mogg, & Bradley, 2005b), smokers (Mogg et al., 2003) and recreational cannabis users (Field, Mogg, & Bradley, 2004a), in other studies with similar users the correlation was absent (e.g. Field, Eastwood et al., 2006; Lubman et al., 2000; Noël et al., 2006). Possibly, craving and attentional bias are not related in all circumstances. However, there are also reasons to believe that craving is just difficult to measure, or sometimes absent while other appetitive motivational processes are present. For example, craving might be low or absent in a clinical setting deprived from substance-related stimuli or perceived availability (Wilson et al., 2004). Secondly, patients might not recognize their craving as such (Johnson, Koob, Schuckit, Mason, & Ait-Daoud, 2006). Finally, craving might be hard to measure since different alcohol abusers may have different craving neuromechanisms (Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005; Potgieter, Deckers, & Geerlings, 1999; Verheul, van den Brink, & Geerlings, 1999), and competing approach and avoidance desires may lead to ambivalence that most craving questionnaires cannot measure (McEvoy, Stritzke, French, Lang, & Ketterman, 2004).

Franken (2003) predicted that craving and attentional bias have a bidirectional causal relationship, strengthening one another. Evidence for the causal role of attentional bias to increase craving was found by Field and Eastwood (2005). They manipulated attentional bias and found subsequent effects on craving and drinking behaviour in heavy social drinkers (see also the paragraph on attentional re-training).

Severity of substance-related problem

Attentional bias for alcohol is related to the quantity and frequency of drinking. Studies often found a higher attentional bias in heavy than light social drinkers (e.g. Townshend &

Duka, 2001) and in alcohol dependent patients than in social drinking control subjects (e.g. Fadardi & Cox, 2006; Stetter et al., 1995). Some studies found a positive correlation between attentional bias and the indices of alcohol consumption (Ryan, 2002; Stetter, Chaluppa, Ackerman, Straube, & Mann, 1994). A number of studies found a correlation with the strength of attentional bias and severity of the drug problem in addicts: attentional bias for alcohol correlated with the number of previous treatments (B. T. Jones, Bruce, Livingstone, & Reed, 2006), and the number of previous detoxifications (Noël et al., 2006). Attentional bias for heroin correlated with the number of months that heroin was used during the year before entering treatment (Bearre, Sturt, Bruce, & Jones, 2007), and attentional bias for smoking correlated marginally significant with years of smoking before treatment (Waters et al., 2003).

Lapse and Relapse

Patients with attentional bias have a greater chance of relapsing into their addiction than patients without attentional bias. One study showed that alcoholic patients whose attentional bias increased during treatment were more likely to relapse during or after treatment than patients whose attentional bias did not change (Cox et al., 2002). In heroin addicts, pre-treatment attentional bias predicted relapse up to three months after treatment (Marissen et al., 2006). Finally, smokers in a cessation clinic who showed a high attentional bias had a heightened risk for lapsing (Waters et al., 2003). In line with this, excessive social drinkers who were motivated to reduce their normal drinking pattern were three times more successful in cutting down when they had a low attentional bias compared to high attentional bias (Cox, Pothos, & Hosier, 2007).

Summary of effects

The empirical evidence on human subjects suggests that attentional bias is related to, and likely causally related to craving, substance abuse and relapse. In addition, attentional bias is not directly targeted by standard treatment programs. Therefore, a treatment tool to directly target attentional bias might be valuable in the treatment of alcohol abuse. Two studies on such a tool - attentional re-training - are presented in Chapters 4 and 5. Training

of attentional bias was first tested in the research domain of anxiety disorders. The next part of the general introduction discusses attention training studies that were conducted previous to our own studies.

Attention Modification Training

Attentional bias can be directly manipulated by a procedure called attention modification training (AMT). On the one hand, this procedure can be used to assess the causal role of attentional bias in cognitive disorders: for example, MacLeod, Rutherford, Campbell, Ebsworthy, and Holker (2002) increased attentional bias for negative words and found an increase in stress reactions in a behavioural test, thus demonstrating the causal role of attentional bias in behaviour. On the other hand, AMT has been studied in a clinically relevant way, to decrease attentional bias in people suffering from cognitive disorders; this is also called 'attentional re-training'. Evidence for the usefulness of AMT to reduce symptoms of mental disorders is scarce; only some authors have referred to clinical AMT studies in anxiety (e.g. De Jong, Kindt, & Roefs, 2006; Mathews & MacLeod, 2002).

MacLeod et al. (2002) subjected participants scoring moderately on emotional vulnerability to a modified version of the visual-probe classification task, i.e. the AMT. The difference with the visual-probe measure is that in the training, in most of the trials (e.g. 90%) probes replaced pictures from only one category (i.e. neutral or disorder-related). Participants were thereby trained to attend to that category and to avoid the other. Participants in the 'attend negative words' group had learned to automatically attend to the threatening stimuli (as measured by the probe classification task) and showed more negative reactions to a subsequent stress task than the attend neutral group. This demonstrated the causal role of attentional bias in vulnerability for anxiety.

To investigate the causal role of attentional bias in addiction, Field and Eastwood (2005) trained one group of heavy drinkers toward alcohol-related pictures and one group away from alcohol pictures. Subsequently, participants rated their urge to drink and performed a bogus taste test: they rated the taste of an alcoholic drink after which the researchers measured the amount of alcohol they had consumed. In subsequent posttests,

the attend group showed a higher attentional bias score, they craved more and drank more compared to the avoid alcohol group.

With the experimental designs used by Field and Eastwood (2005) and MacLeod et al. (2002), it is not possible to determine whether post-test group differences in craving (or stress reactions) and drinking behaviour are caused by an increase in one group, a decrease in the other group, or both. Even changes in variables such as attentional bias that have been pre-tested cannot be definitely attributed to the training. There might have been time-dependent changes in these variables independent of the training, for example by boredom with the task or mere prime effects by exposure to disorder-related cues. In our own studies (Chapters 4 and 5), we have therefore used no-training control groups in which attentional bias was not manipulated.

In the last couple of years, after and during our own re-training studies (Chapters 4 and 5), more research papers on AMT have been published. These are discussed in Chapter 5 and in the general discussion (Chapter 6).

Alcohol prime effects

So far, I have focused on attentional bias in people who were sober at the time of testing. However, research has shown that when people have been drinking the desire for alcohol increases and so does attentional bias (for a review see Field, Schoenmakers, & Wiers, 2008). The effects of alcohol prime doses on appetitive motivational constructs are called 'alcohol prime effects'. These effects are important to understand since they are assumed to be strong predictors of relapse and continued alcohol use.

In the 1970's, studies were conducted in abstinent alcoholics to explain relapse, i.e. continued drinking after a lapse following abstinence. These studies found increases in craving, efforts to obtain alcohol, and speed of drinking following alcohol prime doses in alcoholics in treatment (Bigelow, Griffiths, & Liebson, 1977; Hodgson, Rankin, & Stockwell, 1979; Ludwig & Wikler, 1974). Then, in the nineties, alcohol prime effects have been studied in social drinkers. Main dependent variables in those studies were the desire to drink or craving, and drinking. The first article on prime effects on attentional bias was

published in the next decennium (B. T. Jones & Schulze, 2000). Chapters 2 and 3 describe our studies on prime effects on attentional bias, craving and approach bias (a behavioural tendency to move toward substance-related stimuli) in a laboratory and in a pub.

In order to explain prime effects on the desire for a drug or alcohol, De Wit (1996) has listed several hypotheses. The first is that prime effects are learned responses, derived from either repeated pairings of substance-related objects with effects of the substance (classical conditioning), or derived from the reinforcing effects of consuming the substance on substance seeking (operant conditioning).In the case of classical conditioned effects, cues related to substance use will evoke effects that are similar to effects evoked by the substance itself. In the case of operant conditioned effects, substance-specific effects will stimulate further seeking, since seeking was previously rewarded with these effects. Secondly, prime effects might be explained by unlearned processes, where a substance has incentive properties that lead to more desire for the substance (appetitive motivation). The third hypothesis is that using a substance activates positive memories of past use, acting as motivators to use (memory reactivation). A fourth hypothesis only applies to people who are trying to abstain from substance use. When these people lapse, i.e. use the substance while attempting to quit, they will feel that they have failed in remaining abstinent. This then leads to negative thoughts that interfere with sustained abstinence (abstinence violation effect; Marlatt, 1985). Finally, substances diminish the disinhibition of control over substance seeking; the more you will use, the less you will be able to control your use.

Many laboratory studies have found priming effects of alcohol on the desire to drink in social drinkers. In most of these studies, effects after ingestion of different amounts of alcohol (adjusted for body weight) are compared to a placebo drink (containing no alcohol). De Wit and Chutuape (1993) found that the desire to drink increased after a moderate dose of alcohol (0.5 g alcohol per kg bodyweight[4]) up to 60 minutes after consumption, but not after a low dose of alcohol (0.25 g/kg). Chutuape, Mitchell, and De Wit (1994) found an increase in desire for a low dose 30 minutes after consumption and

[4] 0.5 g/kg is comparable to 2 standard units of alcohol for someone weighing 75 kg. A standard unit is what is mostly served in a pub or restaurant: 1 glass of wine or beer or strong liquid.

higher desire for a moderate dose up to 60 minutes. Duka and colleagues (Duka, Jackson, Smith, & Stephens, 1999) found a borderline significant dose-dependent increase in mild desires for alcohol and decrease in control over drinking after low alcohol doses (0.05, 0.1 and 0.2 g/kg), some minutes after intake. Thirty minutes after intake of a moderate dose (0.6 g/kg), but not a low dose (0.3 g/kg), Rose and Duka (2006) found an increase in craving; 30 minutes later this effect had disappeared.

Apart from these findings, however, two studies found no prime effects on craving. One study reported no effects on craving 20 minutes after finishing a low or moderate dose (Duka & Townshend, 2004). In addition, Schulze and Jones gave participants a fixed amount of alcohol (8 g, corresponding to 0.1 g/kg for someone weighing 75 kg), and found no effects on craving 20 minutes after intake in a first study (1999), but did so in a second study (2000).

Prime effects have also been reported on choosing alcohol over money (Chutuape et al., 1994), but not by (Kirk & de Wit, 2000), drinking more alcohol (de Wit & Chutuape, 1993; Duka, Tasker, & Stephens, 1998), and wanting more alcohol, up to a high dose of 0.8 g/kg (Kirk & de Wit, 2000). Several studies on the moderating influence of stress or medication on alcohol prime effects found similar effects in their control groups (no manipulation of the moderator, thus comparable to the above mentioned studies) after low and moderate doses (Hutchison et al., 2001; Johnson, Campling, Griffiths, & Cowen, 1993; Modell, Mountz, Glaser, & Lee, 1993), and after a high dose (0.8 g/kg, 75 minutes after intake; Soderpalm & de Wit, 2002). Thus, dose-dependent prime effects on desire for alcohol seem to be fairly robust.

Much less research has been conducted on prime effects on attentional bias for alcohol. In the only study reporting prime effects of multiple alcohol doses (Duka & Townshend, 2004), attentional bias showed a different response pattern than the desire for alcohol typically does, which is an increase up to high doses. In that study, attentional bias was higher after a low dose (0.3 g/kg) than after a moderate dose (0.6 g/kg) and placebo. Another study found that social drinkers who were sip-primed with half an English unit of alcohol (approximately 4 g of alcohol) had higher attentional bias scores for positive alcohol-related words than without a sip prime (B. T. Jones & Schulze, 2000). Chapter 2

describes a study in which we measured acute alcohol prime effects on attentional bias, craving and approach bias and eye movements.

In laboratory settings, craving and attentional have been found to increase after a prime dose. It remains to be seen whether these prime effects are still relevant and present in real life. In real life, there are many more influences on drinking behaviour than these appetitive processes. For example, peer influence or habitual consumption. Chapter 3 describes a study in a pub in which craving and attentional bias were measured in relation to the amount of alcohol consumption that evening and normal alcohol use. This thesis thus addresses the question in which way alcohol prime doses increase appetitive motivational processes and whether these effects are present in real life settings. If attentional bias is indeed causally related to addictive behaviours, it is important to understand factors that temporary increase attentional bias and thus further activate substance abuse.

Overview of Chapters

In the first empirical chapter (Chapter 2), I will describe a study on alcohol prime effects on factors of the appetitive motivational system. We hypothesized to find increases in different measures of appetitive motivation and in the correlation between the various constructs. In one session, we gave heavy social drinking participants a low alcohol prime dose, and a placebo drink (no alcohol) in another session. After the drink in each session, attentional bias was measured with a visual-probe reaction time task and eye movements were concurrently measured. Further, we measured subjective craving and approach bias.

In Chapter 3, a field study on alcohol prime effects is presented. We expected craving to increase up to high levels of alcohol use, and we expected attentional bias to increase up to a binge (five drinks for male participants, four for female participants) and to decrease with higher levels of consumption. In two pubs, we measured attentional bias and craving of visitors who had been drinking various amounts of alcohol at the time of testing. In a brief procedure, attentional bias was measured with the Flicker task and craving with a single

item visual analogue scale. The relation between attentional bias, craving, amount of alcohol consumed and normal weekly alcohol consumption was measured.

Chapters 4 and 5 describe studies on the visual-probe version of AMT. We expected a decrease in attentional bias, craving, preference for alcohol over soft drinks and relapse after a clinically designed AMT. In Chapter 4, we re-trained heavy social, male drinkers on attentional bias in the laboratory. In one condition, participants were trained to avoid alcohol-related stimuli and to approach soft drink-related stimuli. In a no-training control condition, participants performed a prolonged visual-probe measure. In the post-test, attentional bias was measured with the visual-probe task for stimuli that were used in the re-training. We further examined generalization of effects in novel stimuli that were not used in the re-training, and with another attentional bias measure, the Flicker task. After the re-training, we also measured craving and preference for either alcohol or soft-drink.

Chapter 5 describes a randomized clinical trial in which we intensified the attentional re-training and tested it on male and female alcoholic patients. The intervention consisted of five sessions in which patients were retrained. The number of training-stimuli was multiplied and patients were given motivational feedback on their performance during the re-training sessions. The control group performed a different reaction time task that would not affect attentional bias, but allowed us to give the same feedback on performance. Post-intervention measures were attentional bias for old and novel stimuli, craving, time to lapse/relapse, and overall treatment success.

Chapter 6 is the general discussion of this thesis. There, I will discuss explanations and findings in alcohol prime studies. Additionally, an important part of that chapter is devoted to new insights on (attend and avoid) AMT, a new model on the underlying mechanisms of avoid-AMT, and further research questions following from a review on the addiction AMT studies that have been published since 2005.

CHAPTER 2
Effects of alcohol priming on appetitive motivation: a lab study

This chapter is based on: Schoenmakers, T., Wiers, R. W., & Field, M. (2008). Effects of a low dose of alcohol on cognitive biases and craving in heavy drinkers. *Psychopharmacology, 197*, 169-178.

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Abstract

Rationale Heavy alcohol drinking increases the incentive salience of alcohol-related cues. This leads to increased appetitive motivation to drink alcohol as measured by subjective craving and cognitive biases such as attentional bias and approach bias. Although these measures relate to the same construct, correlations between these variables are often very low. Alcohol consumption might not only increase different aspects of appetitive motivation, but also correlations between those aspects.

Objective To investigate the effect of a low alcohol dose on changes in various measures of appetitive motivation.

Materials and Methods Twenty-three heavy social drinkers were tested in two sessions, once after receiving an alcohol prime dose, and once after receiving a placebo drink. After drink administration, attentional bias was measured with a visual-probe task using concurrent eye movement monitoring. Furthermore, we measured approach bias with the Stimulus Response Compatibility Task and subjective craving with the Desires for Alcohol Questionnaire.

Results After the alcohol prime dose, participants had higher levels of craving and more pronounced attentional bias (faster reaction times to probes that replaced alcohol rather than control pictures, increased maintenance of gaze on alcohol pictures, and a higher percentage of first eye movements directed toward alcohol pictures). Approach bias was not influenced by the alcohol prime dose. The correlation between attentional bias and approach bias was significantly higher after the alcohol than after the placebo drink.

Conclusions A low alcohol dose increased most measures of appetitive motivation for alcohol and increased the interrelation between cognitive measures of this construct.

According to the incentive sensitization theory (Robinson & Berridge, 1993), after a substantive period of heavy alcohol drinking, cues related to drinking (e.g. beer glasses, wine bottles, a pub) become associated with the effects of alcohol by a conditioning process. During this process, these cues acquire similar appetitive motivational characteristics as alcohol. As a consequence, they become more salient and receive a disproportionate amount of attention (attentional bias). Once attention is focused on the cues other conditioned appetitive motivational responses are triggered, such as craving for the drug and a tendency to have a dominant approach response toward alcohol-related cues, i.e. approach bias. Only heavy drinkers and not light drinkers have been found to show attentional bias (e.g. Townshend & Duka, 2001) and approach bias (Field, Kiernan, Eastwood, & Child, 2008). In this study we examine the effect of a low alcohol dose on measures of appetitive motivation to use alcohol.

Whereas subjective craving is measured with self report questionnaires, cognitive biases such as attentional bias and approach bias are measured with reaction time tasks that reflect relatively automatic and uncontrolled processes. A measure of attentional bias is the visual-probe task, which assesses the allocation of visuo-spatial attention. In this task, two stimuli representing two categories (e.g. alcohol and neutral) are presented simultaneously on a computer screen. After a short interval the stimuli disappear, and a probe (e.g. an arrow) replaces one of the stimuli. Participants respond as quickly as possible to the probe (i.e. identifying the arrow as pointing up or down) by pushing a button. Faster responses to probes replacing alcohol stimuli indicate attentional bias toward alcohol relative to neutral stimuli. Heavy social drinkers typically show attentional bias on longer (500-2,000 ms), but not on short (200 ms) stimulus durations (Field, Mogg, Zetteler, & Bradley, 2004). By contrast, inpatient alcoholics showed attentional bias with a short stimulus duration (50 ms; Noël et al., 2006), but not with longer stimulus durations (Noël et al., 2006; Townshend & Duka, 2007). These findings might be explained as follows. The incentive value of alcohol cues motivates heavy drinkers to maintain their attention on these cues. Ultimately, in alcoholics, the salience of these cues has become high enough to trigger attention automatically, reflected by early engagement of attention toward alcohol cues. The absence of a maintenance bias in alcoholics in treatment might be caused by a strategic

attempt to distract their attention from alcohol cues (Stormark, Field, Hugdahl, & Horowitz, 1997).

Monitoring of eye movements during a visual-probe task sheds further light on the attention process. We will measure eye movements during the visual-probe task since this offers an unambiguous measure of attention compared to the measurement of response latencies. Response latencies only provide an indirect measure of attention and they only inform about the allocation of attention at the time of stimulus offset. In contrast, eye movements are direct manifestations of attention and the monitoring of eye movements offers the possibility of assessing attention during the entire length of stimulus presentation. Attentional bias in eye movements, e.g. prolonged maintenance of gaze ('dwell time') or a higher proportion of initial eye movements directed toward substance-related versus neutral cues, has been demonstrated in tobacco smokers and cannabis users (Field, Eastwood, Bradley, & Mogg, 2006; Field, Mogg, & Bradley, 2004b; Mogg, Bradley, Field, & De Houwer, 2003). However, to date, no investigators have explored attentional bias in eye movements to alcohol-related cues among heavy drinkers.

Approach bias can be measured with the Stimulus Response Compatibility task (SRC; De Houwer, Crombez, Baeyens, & Hermans, 2001; Mogg et al., 2003). In the 'alcohol version' of this task, alcohol-related or neutral pictures appear one by one on a computer screen. Together with these pictures, a manikin is presented. In one block of the SRC task, participants have to move the manikin toward alcohol-related pictures and away from neutral control pictures, thereby measuring approach tendencies. In a second block, this is reversed, thereby measuring avoidance tendencies. The difference in response latencies between the two blocks permits the inference of 'approach bias': if participants are faster in the approach than the avoidance block. In a recent study in which the SRC task was used (Field, Kiernan et al., 2008), only heavy drinkers, but not light drinkers, were significantly faster to approach, rather than avoid alcohol related pictures. Likewise, tobacco smokers were faster to approach, rather than avoid smoking related pictures in the SRC task (Bradley, Field, Mogg, & De Houwer, 2004; Mogg et al., 2003).

A low dose of alcohol has been shown to increase subjective craving for alcohol (Chutuape, Mitchell, & de Wit, 1994; de Wit & Chutuape, 1993; Kirk & de Wit, 2000) and attentional bias - indicated by faster reaction times to probes that replace alcohol-related

rather than control pictures (Duka & Townshend, 2004). There is no evidence yet for effects of an alcohol priming dose on approach bias, although since it also measures appetitive motivation for alcohol use, we expect approach bias to increase after a low alcohol dose. There are numerous explanations for these hypothesised effects, one of which we focus on here. Acute alcohol administration has been found to impair inhibitory control (Fillmore & Vogel Sprott, 1999, 2000, 2006; Fillmore, Vogel Sprott, & Gavrilescu, 1999). When sober, people may use cognitive resources to inhibit automatic responding to the incentive motivational properties of alcohol cues. During alcohol intoxication, however, weakening of inhibitory control might increase automatic responding to the incentive motivational properties of alcohol cues. This leads to the prediction that a priming dose of alcohol should increase the magnitude of attentional bias (as indexed with reaction time measures and eye movements) and approach bias (on the SRC task) for alcohol-related cues.

In line with the incentive sensitization theory (Robinson & Berridge, 1993), craving, attentional bias and approach bias have been theorized to be part of the same general underlying construct, namely appetitive motivation to use alcohol (Wiers, Bartholow et al., 2007). However, there is mixed evidence for the interrelation and co-occurrence of the constructs. As for approach bias, researchers using the SRC and visual-probe task did not find correlations between approach bias and attentional bias for alcohol cues in heavy drinkers (Field, Duka et al., 2007; Field, Mogg, & Bradley, 2005b), but did so for smoking cues in smokers (Mogg, Field, & Bradley, 2005). Subjective craving has been found to correlate with both attentional bias and approach bias for alcohol cues in a number of studies by Field and colleagues (Field, Duka et al., 2007; Field, Kiernan et al., 2008; Field et al., 2005b; Field, Mogg, Zetteler et al., 2004) and with gaze dwell time for smoking cues (Mogg et al., 2005). Using different paradigms, Van den Wildenberg and colleagues (Van den Wildenberg, Beckers, Van Lambaart, Conrod, & Wiers, 2006) did find a correlation between approach associations (measured with the Implicit Association Task) and attentional bias (measured with an alcohol Stroop task) in heavy drinkers. They also found a trend in correlation between craving during the ascending limb of the blood alcohol curve and approach associations before alcohol intake.

Other evidence from studies reporting craving and attentional bias is not conclusive about their relation; many studies found positive correlations (e.g. Franken, Kroon, & Hendriks, 2000; Franken, Kroon, Wiers, & Jansen, 2000), others report no significant correlations (e.g. Ehrman et al., 2002). Field, Mogg, Zetteler et al. (2004) tested correlations between different aspects of attentional bias (measured with a visual-probe task) and craving. In that study, craving was correlated with maintenance of attention (measured by presenting the stimuli for a relatively long duration: 2,000 ms), but not with earlier attention processes, such as a rapid shifting of attention to alcohol-related cues (inferred from reaction times when stimuli were presented for 500 ms and 200 ms). Franken (2003) suggests a bi-directional causal relation between attentional bias and craving. Two studies reported that an experimental increase in attentional bias led to increased subjective craving (Field, Duka et al., 2007; Field & Eastwood, 2005) and drinking (Field & Eastwood, 2005). However, an experimental decrease in attentional bias has not been found to decrease craving or drinking behaviour (Field, Duka et al., 2007; Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007). In sum, there is ample evidence for the interrelation of attentional bias, approach bias and craving, but it is not clear under which conditions these relations are manifest.

We hypothesize that, relative to a placebo, an alcohol priming dose will increase the magnitude of subjective craving, attentional bias, and approach bias. Furthermore, we hypothesise the alcohol priming dose will increase the strength of the correlations between measures of craving, attentional bias and approach bias because alcohol will diminish inhibitory control over performance on these tasks. Performance on reaction time measures is not a purely automatic process, but is partly influenced by inhibitory and attentional control (e.g. Payne, 2005). The type and amount of control that can be exerted likely varies between tasks that require different ways of responding. This may often account for low correlations between different tasks of the same construct. However, when inhibitory control is diminished, performance on these measures should be less determined by control over performance and relatively more by automatic, uncontrolled processes. As a consequence, performance on these tasks will be less determined by construct-'irrelevant' variance, leading to increased construct validity. When the underlying construct of different tasks is the same, performance on these tasks will correlate better. Thus, after an

alcohol prime dose, we expect an increase in the correlation between subjective craving, attentional bias, and approach bias since they are all thought to be outputs of the same underling process, i.e. appetitive motivation for alcohol.

Altogether, the present study investigates the effect of a small alcohol dose in heavy drinkers on attentional bias, approach bias and self reported craving, and correlations between these constructs. We hypothesize that after an alcohol prime, the appetitive motivational system will be sensitized, thereby increasing attentional bias, approach bias and craving. We also test whether the correlations between these measures of appetitive motivation increase after ingestion of the alcohol prime.

Method

Participants

Participants were 23 students (12 males, 11 females) from the University of Liverpool. Their mean age was 20.3 years (standard deviation [SD] = 2.2). They were invited to take part if they self-reported consuming more than 21 (males) or 14 (females) units of alcohol per week. These levels were chosen as they reflect drinking alcohol at levels above those deemed safe by the UK Department of Health (see Edwards, 1996). Weekly alcohol consumption was verified with a self-report questionnaire based on the time-line follow-back procedure (Sobell & Sobell, 1990). On average, male participants drank 43.6 units per week (SD = 13.51; range 23 – 62.5), while females drank 27.2 units per week (SD = 15.75; range 16 – 68). On the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993), male participants scored an average of 15.6 (SD = 5.48; range 8 - 25), while females scored an average of 13.9 (SD = 5.47; range 8 - 27). The range of AUDIT scores indicates that all participants met criteria for hazardous drinking (AUDIT score of 8 or above; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). The experiment received ethical approval from University of Liverpool Committee on Research Ethics.

Materials

The visual-probe and SRC tasks were similar to those used previously, and used the same picture set as in previous studies (Field et al., 2005b; Field, Mogg, Zetteler et al., 2004). This set consisted of 14 pairs of alcohol and matched neutral photographs. Alcohol-related pictures depicted alcohol-related scenes (e.g. a close-up of a female model drinking wine), and each was paired with a control photograph that was matched as closely as possible on perceptual characteristics (e.g. complexity, brightness), but which lacked any alcohol-related content. Another 10 pairs of pictures (not alcohol-related) were selected for practice and buffer trials within the tasks. All pictures were 100 mm high X 125 mm wide. The tasks were programmed in Inquisit version 1.33 and presented on a pentium PC, with 17" VGA monitor, attached to a standard key board. Horizontal eye movements were recorded during the visual-probe task using an infrared head-mounted, Eyetrace 300x system (Applied Science Laboratories, Bedford, MA, USA).

Procedure

Testing took place in a quiet laboratory inside the School of Psychology on the University of Liverpool campus. All participants were tested between noon and 6 P.M.. They were tested twice, with exactly one week between the testing sessions. On one testing day participants received an alcoholic drink; on the other day, a placebo drink. The order of the drinks was counterbalanced between participants.

Participants were asked to refrain from drinking more than three alcoholic drinks the night before each session, not to drink coffee or tea two hours before each session and to have a light meal one to two hours before each session. At the start of the first session, participants gave their informed consent before being weighed and were then breathalysed using a Lion Alcolmeter 500 (Lion Laboratories Ltd., Barry, UK). All participants had a breath alcohol concentration level (BrAC) of 0 at the start of both sessions. Participants then completed questionnaires about their alcohol use and alcohol-related problems (time-line follow back; Sobell & Sobell, 1990) and AUDIT (Saunders et al., 1993). The remainder of the procedure was identical for both testing days.

At time 1, participants completed the 14 item version of the Desires for Alcohol Questionnaire (DAQ; Love, James, & Willner, 1998) and subjective intoxication scales (SIS; Duka, Stephens, Russell, & Tasker, 1998). These were 100 mm visual analogue scales (VAS) which required participants to rate how they felt 'right now' in response to the terms 'lightheaded', 'irritable', 'stimulated', 'alert', 'relaxed', 'contented'. Participants were then administered either the alcohol or placebo drink. All drinks were prepared by a second experimenter and were administered double blind. The alcohol prime consisted of a mix of one part vodka mixed with three parts tonic water and a few drops of Tabasco sauce. All participants received a dose of 0.3 g/kg alcohol, up to a maximum of 100 ml of vodka. The placebo drink consisted of tonic water only, in the same volume as the alcohol mix. A few drops of vodka were smeared on the rim of the glass for each drink. Participants were given 5 minutes to consume the drink, before they rated the strength of the taste of the drink on a Likert scale ranging from 1 ("very weak") to 4 ("very strong") (Field & Duka, 2002). Participants were then allowed to read magazines for 10 min, in order to allow sufficient time for the alcohol to be absorbed.

At time 2 (10 minutes after participants had finished the drink), participants filled out the DAQ and SIS after which the second experimenter came in to measure participants' BrAC. Neither the first experimenter, nor the participant was told the outcome of this measure. Then participants performed the visual-probe task with concurrent eye movement monitoring. Participants were seated 1 m from a computer monitor while wearing eye movement recording goggles and resting on a chin rest. To calibrate the eye monitoring equipment, they were instructed to look at a fixation cross in the center of the screen for 10 s. During the last 5 s of this period their horizontal eye movements were recorded.

Each trial of the visual-probe task started with a central fixation cross for 1,000 ms. Then a picture pair was presented for 2,000 ms, one picture on the left side and one on the right side of the screen, their inner edges 60 mm apart. Immediately after picture offset a probe (an arrow that pointed up or down) appeared in the location that had been occupied by one of the pictures. Before the task, participants were instructed to look at the fixation cross on each trial. As soon as the arrow would appear they had to respond as quickly as possible while trying to avoid making mistakes. Participants responded to the probe by

pressing the corresponding arrow on the keyboard. After each response there was an intertrial interval of 500 ms.

The visual-probe task commenced with 10 practice trials consisting of practice pictures only. Instructions were then clarified before the main task, which consisted of 2 buffer trials, in which the practice picture pairs were again presented, followed by 56 critical trials. All 14 alcohol-control picture pairs were presented four times in the critical trials. Each alcohol picture and control picture appeared twice on the left, and twice on the right side of the screen. Congruent trials (with probes replacing alcohol pictures) and incongruent trials (with probes replacing control pictures) occurred with equal frequency and there were an equal number of probes of each type. The latency and accuracy of participants' responses were recorded. Trials were presented in a new random order for each participant on each testing day.

After completing the visual-probe task, participants removed the eye goggles before completing the SRC task. Each trial of the SRC task started with a blank screen for 1,000 ms. Then, an alcohol or control picture was presented in the centre of the screen and a small manikin was presented either directly above or below the picture. Participants had to move the manikin either toward or away from the picture by using the arrow keys (up and down) on the keyboard. After a correct response the manikin moved toward or away from the picture and then the screen was cleared. If participants made an incorrect response, a large red 'X' appeared in the centre of the screen before the screen was cleared. There was an intertrial interval of 500 ms.

Participants were instructed to categorize pictures appearing on the screen as either alcohol-related or unrelated to alcohol by moving the manikin. They were further instructed to respond as quickly as possible without making mistakes. The SRC task consisted of two blocks. In the 'approach alcohol' block, participants had to move the manikin toward the alcohol pictures and away from the non-alcohol-related pictures. In the 'avoid alcohol' block, these instructions were reversed. Each block commenced with 8 practice trials consisting of 4 alcohol-related and 4 control pictures. Instructions were then clarified before the main part of a block, consisting of 56 critical trials. During the critical trials, 14 alcohol and 14 control pictures were presented 4 times each: twice with the manikin above each picture, and twice below. The latency and accuracy of participants'

responses were recorded. Trials were presented in a new random order for each participant on each testing day. The order of presentation of 'approach alcohol' and 'avoid alcohol' blocks was counterbalanced across participants, and block order remained the same across the two testing sessions.

Upon completion of these tasks, once again they filled out the DAQ and SIS (time 3). Participants were then asked to estimate how many standard 25 ml 'shots' of vodka had been in their drink (0, 1, 2, 3, 4, or more), before being breathalysed by the second experimenter again. Before being discharged, participants were advised to remain in the laboratory until their BrAC had dropped down to zero, and they were advised not to drive, ride a bike or operate any kind of machinery for the remainder of the day. During the second testing session, the above procedure was repeated with the exception that participants received a different drink (alcohol or placebo). Before being discharged, participants were fully debriefed and given £20 UK sterling as compensation for their time and expenses.

Data analyses

Eye movements

Eye movement data were analyzed using Orbit EyeTrace software (IOTA AB, Sweden). Eye movements during the visual-probe task were measured to the regions of the screen that corresponded to those occupied by alcohol and control pictures, and the centre region. The position of gaze was measured every 8.3 ms (120 Hz) during the 2,000 ms stimulus presentation in each trial. For each trial we calculated the total time (in ms) in which gaze was directed at one of the three regions, which permitted us to calculate gaze 'dwell time' on alcohol-related and control pictures. The first eye movement was defined as the first fixation of at least 100 ms duration in the region of either the alcohol or control picture, at least 100 ms after picture onset and before picture offset. This permitted us to calculate the percentage of initial eye movements that were directed at alcohol-related versus control pictures during the task. Due to a technical failure, we lost information about the position

of alcohol and control pictures for one participant. Therefore, we could not interpret her eye movement data and visual-probe reaction time data.

Data distribution

Outlying reaction time (RT) data from the SRC task were removed when they were more than 2,000 ms or less than 200 ms, and when they were more than 3 SDs above the mean for each participant. Visual-probe RT data were positively skewed; to reduce the effect of outlying data points median reaction times were calculated for congruent and incongruent trials. All dependent variables were then checked for normality. Responses on the subjective intoxication scales in both sessions, and mean gaze 'dwell time' for alcohol pictures were not normally distributed and could not be transformed to normality using log or square root transformations. Therefore, nonparametric tests were used to analyze these variables.

Session order

Session order (alcohol first, then placebo, or vice versa) was counterbalanced between participants. To check whether effects differed between each order, we used session order as a between subjects variable in our analyses of the DAQ, visual-probe RT and SRC task. Session order did not contribute significantly to any of these analyses. For the other dependent variables, scores for each session order group were compared: nonparametric Mann-Whitney tests for gaze dwell time and the difference scores from time 1 to time 2 for SIS; independent-samples t-tests on first eye movement, 'taste of drinks' and 'alcohol content'. None of these tests were significant. Session order was therefore excluded from all further analyses.

Results

Manipulation checks

Subjective Intoxication Scales

We performed nonparametric Wilcoxon signed-rank tests to compare differences within sessions (from time 1 to time 2) and across sessions for VAS ratings of 'lightheaded', 'irritable', 'stimulated', 'alert', 'relaxed', and 'contented'. In both sessions lightheadedness increased after drink administration (i.e. from time 1 to time 2), but lightheadedness at time 2 in the alcohol session was higher than in the placebo session, $z = 3.18$, $p < 0.01$. Alertness decreased significantly in the alcohol session after the drink (see Table 2.1 for more details).

Taste of drinks and perceived alcohol content

To check whether participants were aware of the difference between the alcohol and placebo drink we performed paired-samples t-tests on perceived strength of the drinks and perceived number of vodka shots in the drinks. They perceived the alcoholic drink to be significantly stronger and to contain more vodka shots than the placebo drink, $t(22) = 4.41$, $p < 0.01$, $t(22) = 4.41$, $p < 0.01$, respectively.

Breath alcohol concentration level (BrAC)

The BrAC for all participants was 0 mg% at time 1 in both sessions and at time 2 in the placebo session. In the alcohol session at time 2, the average BrAC was 0.40 mg% (SD = 0.23) and declined to 0.30 mg% (SD = 0.13) at time 3.

Table 2.1

Nonparametric Wilcoxon signed rank tests of the SIS in alcohol and placebo session from time 1 to time 2

	Time 1		Time 2		Time 1 compared with Time 2
	Mean	SD	Mean	SD	Z
Alcohol session					
Lightheaded	14.85	21.94	33.40	25.75	3.06***
Irritable	9.99	20.16	10.95	16.08	0.51
Stimulated	30.17	29.53	38.51	23.47	1.92
Alertness	58.18	19.78	48.18	23.03	2.56**
Relaxed	55.91	24.27	59.82	25.82	1.29
Contented	54.29	24.61	51.91	25.51	0.67
Placebo session					
Lightheaded	11.62	19.41	17.45	23.96	1.96*
Irritable	16.20	22.62	12.62	14.73	1.30
Stimulated	27.55	26.04	34.46	27.62	1.85
Alertness	49.43	27.41	46.07	22.70	1.53
Relaxed	56.42	19.92	54.97	18.51	0.29
Contented	52.23	22.84	51.92	21.60	0.35

Note Scores are means and SDs from 100 mm VAS.

* p < .05; ** p <.01; *** p < .001.

Craving (Desires for Alcohol Questionnaire)

We compared differences in mean DAQ scores with a repeated measures ANOVA with time (time 1, time 2) and session (alcohol, placebo) as within subjects variables. The interaction time x session was significant, $F(1,22) = 6.39$, $p = 0.02$. Post-hoc tests revealed a significant increase in DAQ scores during the alcohol session from time 1 to time 2, $t(22) = 2.64$, $p = 0.03$. There was, however, no such increase in the placebo session, $t(22) = 1.09$, $p = 0.58$ (see Table 2.2).

Visual-probe task reaction times

Because of technical problems, we lost visual-probe reaction time data from one participant. Due to errors, 1.5 percent of the data was removed. We performed a repeated measures ANOVA with trial type (congruent, incongruent) and prime session (alcohol, placebo) as within subjects variables. The two-way interaction was significant, $F(1, 21) = 5.85$, $p = 0.03$. Paired-samples t-tests revealed a significantly faster reaction time for congruent than incongruent trials in the alcohol session, $t(21) = 2.20$ $p = 0.04$, indicating an attentional bias. In the placebo session there was no such effect, $t(21) = .20$, $p = 0.85$ (see Table 2.2 and Figure 2.1).

Gaze dwell time

Data were not normally distributed and data could not be transformed to normality. We performed nonparametric Wilcoxon signed-rank tests to compare differences between mean gaze 'dwell time' on alcohol and control pictures during trials of the visual-probe task in each session. In the alcohol session, dwell time on alcohol pictures was significant longer than dwell time on control pictures, $z = 2.32$, $p = 0.02$. In the placebo session there was no difference between alcohol and control pictures, $z = 1.08$, $p = 0.28$ (see Table 2.2 and Figure 2.2).

Table 2.2

Means and SDs for measures of appetitive motivation during alcohol session and placebo session: craving (DAQ), attention (visual-probe reaction times, mean gaze 'dwell time', first eye movement), and approach/avoidance (SRC task reaction times).

	Placebo session		Alcohol session	
	M	SD	M	SD
Craving				
DAQ score at time 1	2.56	1.02	2.67	0.96
DAQ score at time 2	2.65	1.18	3.04	1.16
Visual-probe task				
Median reaction time on congruent trials (ms)	635	13.2	639	15.8
Median reaction time on incongruent trials (ms)	634	13.3	660	15.3
Mean gaze 'dwell time' on alcohol pictures (ms)	775	129	812	193
Mean gaze 'dwell time' on control pictures (ms)	740	146	709	141
Percentage first eye movements toward alcohol pictures	49.5	5.40	53.9	8.56
SRC task				
RT during 'approach alcohol' block (ms)	720	102	722	103
RT during 'avoid alcohol' block (ms)	761	105	743	75.3

Note DAQ is the mean score on the Desires for Alcohol Questionnaire at time 1 (before drink administration) and time 2 (after drink administration), scale 1-7.

Figure 2.1
Visual probe task reaction time

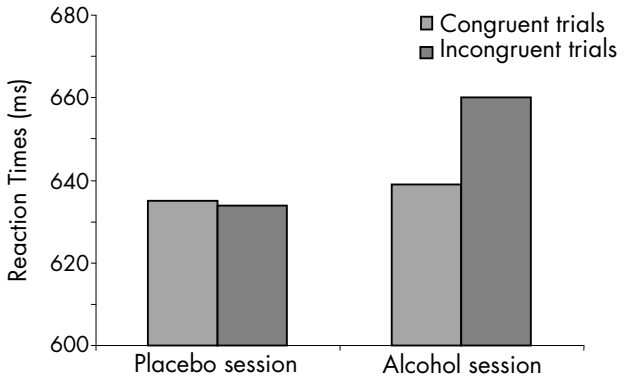
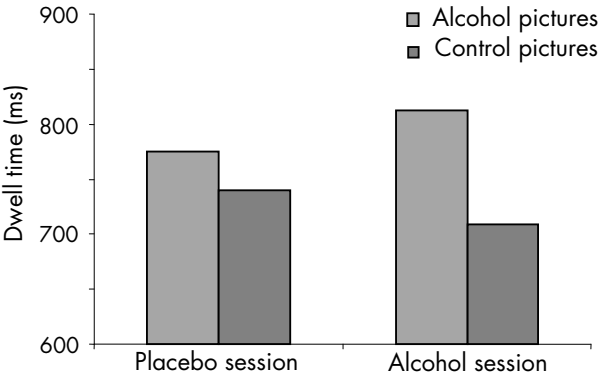


Figure 2.2
Visual probe task mean gaze 'dwell time'



Direction of first eye movement

To examine whether participants showed a bias in first eye movement direction during the visual-probe task, the percentage of first eye movements toward alcohol pictures was compared with 50 % (which indicates no bias). After the alcohol prime, this percentage was significantly greater than 50 percent, $t(21) = 2.12$. $p = 0.05$. After the placebo prime, the percentage did not differ significantly from 50 %, $t(21) = -0.43$, $p = 0.68$ (see Table 2.2). Also, a dependent t-test revealed that first eye movement percentages toward alcohol pictures significantly differed between prime sessions, $t(21) = 2.15$, $p = 0.04$.

SRC task

Due to errors, 3.4 % of the data was excluded, and a further 2.7 % was also excluded due to outliers. Data from two participants were excluded because they had an outlying high error rate and data from one further participant were excluded due to outlying mean reaction times in the avoid alcohol block. Data were analyzed using a 2 x 2 x 2 mixed design repeated measures ANOVA, with SRC block ('approach alcohol', 'avoid alcohol') and prime session (alcohol, placebo) as within subjects factors and order of block (first block: 'approach alcohol', first block: 'avoid alcohol') as between subjects factor. This three way interaction was not significant $F(1, 18) = 1.05$, $p = 0.32$. The hypothesized interaction of session x SRC block was not significant either, $F(1, 18) = 2.62$, $p = 0.12$ (see Table 2.2). There was a significant main effect of SRC block, $F(1, 18) = 7.63$, $p = 0.01$, as participants were significantly faster during the 'approach alcohol' block compared to the 'avoid alcohol' block, indicating an approach bias in both sessions.

Correlations between dependent variables

To test whether correlations between measures of appetitive motivation increase after ingestion of the alcohol prime, we compared the strength of correlations in the alcohol session with those in the placebo session. First, we computed the five relevant variables; attentional bias RT was calculated by subtracting mean reaction times on congruent trials from incongruent trials, separately for each session. Mean gaze 'dwell time' bias was calculated by subtracting mean dwell time on neutral pictures from alcohol pictures for

each session. Approach bias was calculated by subtracting mean reaction times from the 'approach alcohol' block from mean reaction times from the 'avoid alcohol' block in the SRC task for each session. Original scores of first eye movement percentage toward alcohol cues and craving scores at time 2 were correlated as well. Mean gaze 'dwell time' bias was not normally distributed; therefore, we calculated Spearman correlations (ρ) for this bias with the other variables. For all other correlations we used Pearson's test (r).

Attentional bias RT and mean gaze 'dwell time' bias were significantly correlated in the alcohol session, $\rho = 0.52$, $p = 0.01$, as well as in the placebo session, $\rho = 0.45$, $p = 0.04$. Further, attentional bias RT and approach bias were stronger correlated in the alcohol session than the placebo session, $r = 0.51$, $p = 0.03$, $r = 0.05$, $p = 0.83$, respectively. A greater range for attentional bias RT and approach bias in the alcohol session might be responsible for the increased correlation between those variables. Therefore, we tested whether the correlation in the alcohol session would be much different from the placebo session when measured with a more conservative nonparametric rank test. This was not the case; Spearman's correlation in the alcohol session was 0.40 ($p < 0.10$), and in the placebo session 0.08 ($p > 0.50$). Using Steiger's test for calculating differences between correlations (Steiger, 1980), we found that the Pearson correlation was significantly higher in the alcohol than the placebo session, $z = 1.70$, $p = 0.04$, indicating a significant increase in the correlation between these cognitive biases after the alcohol prime dose.

The previous finding is consistent with the difference in correlations between mean gaze 'dwell time' bias and approach bias (alcohol session: $\rho = 0.51$, $p = 0.03$; placebo session: $\rho = -0.21$, $p = 0.40$), $z = 2.38$, $p = 0.01$. All other correlations within the sessions were non-significant (all over $p > 0.05$) and did not differ significantly between sessions (all over $p > 0.05$). See Table 2.3 for a correlation matrix for the dependent variables per session.

Table 2.3

Correlations between dependent variables for the alcohol and placebo session

	1		2		3		4	
Measures	A	P	A	P	A	P	A	P
Attentional bias								
1. Reaction time	-	-						
2. Mean gaze dwell time	0.52*	0.45*	-	-				
3. Percentage first eye movements toward alcohol	0.11	-0.31	0.30	0.10	-	-		
Other								
4. Approach bias	0.51*	0.05	0.51*	-0.21	0.30	-0.06	-	-
5. Craving time 2	0.25	-0.09	0.28	0.17	0.04	-0.31	0.21	0.39

Note Correlations with mean gaze dwell time bias are nonparametric Spearman correlations. All other are parametric Pearson correlations.
A: correlations for the alcohol session, P: correlations for the placebo session.

Discussion

In this study we found that multiple indices of attentional bias were significantly larger after a low alcohol dose compared with placebo. This effect was apparent in reaction time latencies during the visual-probe task as well as in concurrent dwell time measures. Additionally, in contrast to the placebo, the percentage of first eye movements toward alcohol cues was higher and significantly above chance level after the alcohol prime. Unexpectedly, approach bias did not differ as a function of alcohol consumption; a significant approach bias for alcohol was found in both sessions. As hypothesized, craving significantly increased after the alcoholic drink, but not after the placebo drink. In line with our hypothesis, correlations between measures of appetitive motivation were mostly higher in the alcohol than the placebo session. However, these differences only reached significance for the correlations between attentional bias RT and mean gaze dwell time bias with approach bias. As compared to earlier research into the effects of alcohol intake on appetitive motivation, our results give a more detailed insight. This is because we integrated different measures from earlier research (attentional bias RT and craving) and added new ones (eye movement monitoring and approach bias).

The increase in attentional bias after a low alcohol dose is consistent with results of Duka and Townshend (2004), who found an increase after an identical dose. A difference with their study is that they used a shorter stimulus presentation duration of 500 ms, whereas ours was 2,000 ms, showing that the increase in attentional bias for alcohol-related stimuli is maintained when pictures are presented for 2,000 ms. Mean scores of congruent and incongruent trials (Table 2.2) show that the effect was mainly caused by participants being slower on incongruent trials in the alcohol session compared to the placebo session. This indicates that the prime dose hampered attentional disengagement from alcohol-related stimuli (cf. Koster, Crombez, Verschuere, & De Houwer, 2004) at stimulus offset.

In addition to assessing attentional bias through an indirect measure (visual-probe task response latencies, we measured attention directly through monitoring participants' eye movements during the visual-probe task. This allowed us to monitor attention not only at stimulus offset (as with response latencies) but rather during the entire length of the

stimulus presentation. The finding that after the alcohol dose, the dwell time and first eye movements toward alcohol cues increased, suggests that both initial engagement as well as the maintenance or disengagement of attention are sensitive to an activated motivational state. Further, we think that the alcohol dose sensitized the heavy drinkers in such a way that their attentional bias became more automatic, as indicated by initial orienting of attention to alcohol-related stimuli, and thereby more similar to that of alcoholics (see Noël et al., 2006).

Regarding the SRC task, participants showed an approach bias, although this effect was not significantly influenced by the alcohol prime. It is interesting to note that, in a previous study with smokers (Field, Mogg, & Bradley, 2005a), administration of an alcohol priming dose led to increased attentional bias for smoking-related cues (as inferred from reaction times to probes, and gaze 'dwell times'), but did not influence the tendency to direct approach responses toward those cues during the SRC task. Therefore, it seems that alcohol priming doses may increase the 'attention-grabbing' properties of drug-related cues, without influencing the tendency to direct rapid approach responses toward those cues. Specifically, approach bias appears to be a more stable construct than attentional bias, in that it is not influenced by an alcohol priming dose. However, approach bias does correlate with aspects of attentional bias, but only when the individual is intoxicated.

Rather than physically approach or avoid stimuli in the SRC task, participants symbolically move a small manikin toward or away from the stimuli. For this reason, one might question the validity of the SRC task for measuring approach and avoidance tendencies. Recent studies suggest, however, that it is not the physical movement toward or away from stimuli that is responsible for the performance on an approach/avoidance task, but the cognitive representation of an approach or avoid action (Lavender & Hommel, 2007; Markman & Brendl, 2005). Instructing participants to approach by moving the manikin toward stimuli and to avoid by moving it away forms a cognitive representation of approach and avoid. We believe this representation determines the approach bias that we observed in the present study as well as in other studies that used the SRC task with tobacco smokers (e.g. Bradley et al., 2004; Mogg et al., 2003).

Craving and first eye movements changed parallel to factors of attentional maintenance, although a direct relation between these factors in terms of correlations was

not observed. A possible reason is that there are individual differences in the way different factors of appetitive motivation react to an alcohol prime. Thus, overall there was an increase in most of our dependent variables after alcohol, but there might be inter-individual differences in the extent to which this increase manifests itself in different aspects of self-report and cognitive processing.

In the present study, there were no significant correlations between craving and cognitive biases in both sessions. In this regard, the previous evidence is mixed, as some studies demonstrate a clear relationship between cognitive biases and subjective craving whereas others do not (see introduction). Some theorists have argued that subjective craving and the incentive-motivational properties of drug-related cues are not always related. Robinson and Berridge (2000) state that "...the neural system responsible for incentive salience attribution can sometimes produce goal directed behavior....in the absence of conscious awareness of "wanting"..." (p. S105). In addition, Wiers and colleagues (Wiers, Bartholow et al., 2007) propose a model in which subjective craving is not necessary for biased cognitive processing of drug cues to occur in heavy substance users. We did find an increase in subjective craving, so there seemed to be at least some conscious awareness of "wanting". However, since significant correlations with craving were absent, one may question whether our craving measure and cognitive bias measures tapped the same underlying construct.

In our introduction we offer one possible explanation for the alcohol prime dose effect, namely disinhibition of control. The goal of our study was to specify the effect, not to directly test the disinhibition hypothesis. To test this tentative explanation, further research should correlate individual differences in inhibitory control with individual differences in cognitive bias, when participants are both intoxicated and sober.

To conclude, different measures of appetitive motivation react differently to an alcohol prime dose. Whereas subjective craving, attentional maintenance and initial engagement toward alcohol cues increased, approach bias did not change. We suggest that further research should focus on differences and similarities between attentional and approach bias in response to alcohol prime doses and their possible mediation by deficits in inhibitory control.

CHAPTER 3

Effects of alcohol priming on craving and attentional bias: a field study

This chapter is based on: Schoenmakers, T., & Wiers, R. W. (under review). Craving and attentional bias respond differently to alcohol priming: a field study in the pub.

Abstract

Background: Subjective craving for alcohol has been found to increase with increased alcohol ingestion. Less is known about alcohol prime effects on relatively automatic appetitive motivational processes such as attentional bias (AB). Alcohol prime experiments have been mainly performed in laboratories. It is not known whether the effects can be generalized to real drinking environments, and whether effects change after higher alcohol doses than those that have been administered in lab studies.
Aims: To investigate alcohol prime dose effects in craving and AB in a real life setting.
Setting: Two pubs in Limburg, the Netherlands.
Participants and design: Seventy-two social drinkers on a night out, opportunistically sampled. They had been drinking various amounts of alcohol and were each tested once.
Measurements: Social drinkers were tested on subjective craving and AB, measured by a modified Flicker Paradigm.
Findings: Craving was positively predicted by dose of alcohol consumed, from one up to 16 drinks. In contrast, AB was negatively predicted by dose consumed in participants who had been binge drinking.
Conclusions: While the desire for alcohol increased even after very high levels of alcohol ingestion, AB decreased dose-dependently in the group of participants who had been binge drinking that night. In the discussion we offer two possible explanations for these dissimilar prime effects in these aspects of appetitive motivation. This field study validates earlier experimental research on alcohol prime effects in a real drinking situation. Further, it demonstrates prime effects up to much higher alcohol doses than in previous lab studies.

Binge drinking increases the risk for alcohol-related problems. Potential problems as a direct result of one binge episode include aggressiveness, sexual risk taking, school or work-related problems, and medical problems (Wechsler & Nelson, 2001). Although social drinkers are aware of these negative consequences, their motivation to drink does not necessarily decrease after a few glasses of alcohol. This continued drinking might partly result from an increased desire or motivation to drink as an acute prime effect of alcohol intake. Alcohol prime effects have been hypothesized to be classical conditioned responses to alcohol cues, instrumentally learned responses to the act of drinking, and/or unlearned motivational responses to appetitive stimuli like alcohol. Additionally, drinking alcohol might activate positive memories of past drinking, which act as motivators to drink (de Wit, 1996)

Dual process theories consider drinking motivations as originating from two kinds of appetitive processes. These are explicit, deliberate motivations to drink, e.g. subjective craving, and implicit, relatively automatic cognitive processes, such as attentional bias (AB) (Kavanagh, Andrade, & May, 2005; Robinson & Berridge, 1993). AB for alcohol is demonstrated when a person attends longer or faster towards alcohol-related cues compared to neutral cues in a reaction time task. This indicates that alcohol cues have incentive salience. As a result, these cues receive a disproportional amount of attention, which potentially leads to increased craving and drinking (Field & Eastwood, 2005; Franken, 2003).

Although subjective craving and AB are both related to the motivation to drink alcohol, they do not necessarily react in a similar way to alcohol prime doses (Duka & Townshend, 2004). In addition, the evidence for correlations between the two constructs, measured in sober participants, is rather mixed. A number of studies found that craving and AB were correlated (see Field, Mogg, & Bradley, 2006 for an overview), but there have also been several studies reporting no significant correlation (Ehrman et al., 2002; Lubman, Peters, Mogg, Bradley, & Deakin, 2000; Noël et al., 2006; Schoenmakers, Wiers, & Field, 2008; Waters et al., 2003). In brief, since craving and AB do not appear to be consistently related, they might also react differently to various prime doses.

As for subjective craving or desire for alcohol, prime effects seem to be fairly robust and dose-dependent. In most studies, effects after ingestion of different amounts of alcohol are

compared to a placebo drink (containing no alcohol). With prime doses ranging from low (0.05 – 0.3 g alcohol per kg body weight) to moderate (0.5 - 0.6 g/kg) and high (0.8 g/kg), subjective craving has been found to be higher for larger doses at different time intervals up to one hour after intake (Chutuape, Mitchell, & de Wit, 1994; de Wit & Chutuape, 1993; Duka, Jackson, Smith, & Stephens, 1999; Rose & Duka, 2006; Schoenmakers et al., 2008; Schulze & Jones, 2000). In contrast to these findings, two studies found no prime effects on craving (Duka & Townshend, 2004; Schulze & Jones, 1999). Prime effects on other indicators of the desire to drink have also been reported, for instance on choosing alcohol over money (Chutuape et al., 1994), but not by Kirk and De Wit (2000), drinking more alcohol (de Wit & Chutuape, 1993; Duka, Tasker, & Stephens, 1998), and wanting more alcohol (Kirk & de Wit, 2000). Altogether, we expect a positive relationship between craving ratings for alcohol and the amount of alcohol consumed.

The scarce results on AB suggest a different response pattern to various prime doses than the desire for alcohol typically shows. In the only study reporting prime effects after multiple alcohol doses, AB was higher after a low dose (0.3 g/kg) than after a moderate dose (0.6 g/kg) and placebo (Duka & Townshend, 2004). A study that compared a placebo to a low alcohol dose replicated these results for the low dose (Schoenmakers et al., 2008). By monitoring eye movements, the latter study also found a concurrent increase in gaze dwell time and in the percentage of first eye movements towards alcohol-related stimuli. A third study found that social drinkers who were primed with half an English unit of alcohol (approximately 4 g of alcohol, a low dose) had higher AB scores for positive alcohol-related words than without a sip prime (B. T. Jones & Schulze, 2000). Based on this evidence we expect a positive relationship between AB scores and amount of alcohol consumed in people that have been drinking low to moderate doses, and a negative relationship for higher doses.

All these reported studies on prime effects are controlled laboratory experiments. It might be questioned, though, to what extend the results from these studies can be generalized to real world drinking settings in which many more uncontrolled factors might influence drinking motivation. Firstly, the interior of common drinking environments differs from the interior of labs. In a meta-analysis, McKay and Schare (1999) found that compared to normal labs, alcohol effects on expectancies and pharmacological reactions

were larger in natural environment labs. This was explained by the presence of environmental cues that are also encountered during normal alcohol consumption, and a greater relaxation in participants. Secondly, the amount of alcohol consumed in a real world drinking setting often exceeds the amount of alcohol in the experimental priming studies. Consequently, knowledge about alcohol prime effects thus far is limited to effects of relatively modest alcohol doses.

The present study investigated alcohol prime effects in a natural drinking environment. Our participants did not ingest standardized amounts of alcohol as in laboratory studies, but had already been drinking various amounts during a normal night out when they were invited to participate. To prevent disrupting participants' natural drinking behaviour, we designed a very brief study procedure and each participant was tested once. Aim of the study was to test the generalizability of prime effects to uncontrolled, real world drinking settings. This could validate the alcohol prime research thus far, and extend it to higher alcohol doses than have been administered in the lab. To recapitulate: we hypothesized that craving ratings would show a positive relationship with reported amounts of consumption. Further, we hypothesized that AB scores would show a positive relationship with amount of consumption up to moderate doses, and a negative relationship from moderate to higher doses.

Methods

Participants

We recruited an opportunistic sample of visitors (58 male, 22 female) of two pubs in Maastricht and Sittard, Limburg, The Netherlands. Two participants who indicated to never drink (abstainers) and six participants who had not been drinking in the last hour were excluded from analyses. 90 Percent of participants had taken their last sip from an alcoholic drink less than 20 minutes ago. Further descriptives of participants are summarized in Table 3.1. The research performed in the present study received ethical approval from the Ethics Committee of Psychology from Maastricht University.

Table 3.1

Characteristics of participants and drinking-related data, separated by gender.

	Males (N=55)			Females (N=17)		
Variable	M	SD	Range	M	SD	Range
Age	28.24	6.52	18-46	26.29	5.95	18-38
'Normal use'	15.91	12.15	1-60	9.18	9.28	1-38
'Drinks today'	6.43	3.91	1-16	3.68	3.23	1-14
BrAC at time of testing	0.53	0.42	0-1.9	0.35	.39	0-1.54
Time elapsed since last sip	5.32	11.01	0-60	5.53	9.84	0-30

Note 'Normal use' (normal weekly consumption) and 'drinks today' (number of drinks consumed at time of testing) are in Dutch standard units (10 g of alcohol); BrAC (Breath alcohol concentration) is in mg/l; time since last sip is in minutes.

Materials

Stimuli for our AB measure - the Flicker Paradigm - were full-colour photographs (646 x 484 pixels). Figure 3.1 shows the originating stimuli and the changed stimuli of the critical and practice trials. For the critical trials, the alcohol-related objects were positioned left from the center of the photographs, and the neutral objects (stationery) right from the centre. This composition was reversed for half of the participants. In the practice photograph, there were no alcohol-related objects. It consisted of neutral objects (spices) unrelated to the neutral category in the critical trials. The mask consisted of a screen full of Xs. The task was programmed in Inquisit 2.0 (Millisecond Software) and presented on a Fujitsu Siemens Lifebook C Series laptop computer with a 22 x 29 cm screen size. The stimuli, sized 13.5 x 17 cm, were presented centralized on the screen. Viewing distance was approximately 40 cm.

Figure 3.1
Stimuli for the Flicker task: critical trials left, practice trial right.

Originating stimulus

Originating stimulus

Changed Stimulus, alcohol trial:
Outer left bottle is reversed

Changed stimulus:
Black jar is reversed.

Changed Stimulus, neutral trial:
Outer right book is reversed

Procedure

Participants were tested on a Thursday, Friday or Saturday between 7 PM and midnight. Testing took place in the back of two pubs, where it was relatively quiet. Visitors of the pubs were approached by the researchers and asked whether they were interested in participating in a brief experiment on attentional processes and alcohol use. When participants agreed to participate, they gave informed consent and agreed not to drink during the remainder of the procedure. Participants did not receive any compensation for participating. All participants were tested separately, without immediate presence of other participants.

First, participants were asked how many minutes ago they had taken their last sip of alcohol, and how many drinks they had consumed in total ('drinks today'). Then, they indicated their normal alcohol use in units per week ('normal use'). Units were defined as Dutch standard drinking units of 10 g of alcohol. Before measuring their breath alcohol concentration (BrAC), participants had to rinse their mouth thoroughly with water to remove any remaining alcohol. BrAC was measured with a Lion Alcometer SD-400. After the BrAC measurement participants rated their urge to 'drink alcohol right now' (craving) on a 100 mm visual analogue scale, ranging from "no urge at all" to "an almost irresistible urge" (Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996).

Lastly, AB was measured with a modified Flicker Paradigm to induce change blindness (Bearre, Sturt, Bruce, & Jones, 2007; B. T. Jones, Bruce, Livingstone, & Reed, 2006; B. T. Jones, Jones, Smith, & Copley, 2003; Rensink, O'Regan, & Clark, 1997; Yaxley & Zwaan, 2005). An advantage of this task is that it takes very little time to administer. In our version of the Flicker task, participants were instructed to detect a changing object within a picture as fast as possible. A trial of the task started with an originating stimulus picture for 250 ms, than a mask for 80 ms, followed by a changed stimulus picture for 250 ms, than the mask for 80 ms again. This loop was repeated until the participant pressed a response button to indicate that he or she had detected the difference between the two pictures. Participants then indicated the position on the screen where they had spotted the change and described the object that they had seen changing. Participants performed three Flicker trials. The first

trial was a practice trial, with a change in the centre of the picture to avoid creating expectancies about the change location in the later trials. In the subsequent alcohol trial, an alcohol-related object was turned in the changed stimulus picture. In the neutral trial, a neutral object was turned in the changed stimulus picture. For each individual participant, the originating stimulus picture was identical in the alcohol and neutral trial. Participants were randomly assigned to the version of the task with either alcohol left or right from the centre.

AB was calculated by subtracting the response latency in the alcohol trial from the response latency in the neutral trial. We expected that, through practice, participants would be faster in the second than the first critical trial. Therefore, the order of trials was not counterbalanced between subjects. Every participant first performed the alcohol change trial and then the neutral change trial[5]. After the Flicker task, participants were debriefed and thanked.

Data analyses

Prime effects were calculated in hierarchical regression analyses, separately for craving and AB. As predictors in these analyses, we included usual drinking behaviour ('normal use') and gender in the first step, and added the number of drinks that participants had drunk at the testing day ('drinks today'), the elapsed time (in minutes) since the last sip, and breath alcohol concentration (BrAC) in the second step. For all regression analyses, factors with *p*-values over 0.30 were excluded and not reported.

[5] As a consequence, the absolute value for the attentional bias score might be an underestimation of the 'real' attentional bias score. In this study, however, the absolute value was irrelevant, and the neutral trial has been used purely to control for inter-individual differences in change detection ability.

Results

Craving

One influential case was removed based on its Cooks distance. 'Drinks today' significantly predicted urge, confirming our hypothesis that craving increases dose-dependently even up to very high alcohol doses. The positive effect of 'normal use' on craving indicates that heavier drinkers experience more craving than lighter drinkers. The results are shown in Table 3.2.

Table 3.2

Summary of hierarchical regression analysis predicting the urge to drink alcohol.

Step	Variable	β	SE β	*p*
1	'Normal use'	0.48	0.11	<0.001
2	'Normal use'	0.41	0.10	<0.001
	'Drinks today'	0.24	0.10	0.020
	Time elapsed since last sip	-0.19	0.10	0.064

Note N=71. R^2=0.21 for step 1, R^2change=0.14 for step 2. Final model: R^2=0.35, p<0.001.

Attentional bias

Preparation of data We expected a different pattern in AB for participants who had been drinking low doses of alcohol than for those who had been drinking moderate to high doses. Therefore, the hierarchical regression analysis was done separately for participants who had binged and participants who had not binged at the time of testing. A binge was defined as having drunk more than five units (four for females) (Wechsler & Nelson, 2001). For each participant, AB was calculated by subtracting the response latency in the alcohol trial from the response latency in neutral trial. Therefore, only participants who reported

the correct position and object of change in both critical trials of the Flicker task were included in the analyses, leaving 24 bingers and 24 non-bingers for the analyses. To check whether these participants differed from the excluded participants on any of the predictors, we performed non-parametric Mann–Whitney tests separately for the binge and non-binge group. None of these comparisons was significant (all over $p > 0.40$).

Results Three influential cases (Cook's distance) were removed from analysis in the non-binge group. Contrary to expectations, Table 3.3 shows that 'drinks today' did not predict AB in the group of non-bingers. As hypothesized, in the group bingers, AB was negatively predicted by 'drinks today', indicating that AB decreased with increased consumption levels (Table 3.4). In both groups, AB was positively predicted by 'normal use', indicating that AB was higher for participants with heavy normal use than for those with light normal use.

A possible confound in the assessment of AB in the binge group is a slow down in reaction time caused by alcohol (Kerr & Hindmarch, 1998). However, since AB is a difference score, the effect of variable reaction times between participants is controlled. Moreover, there was no correlation between 'drinks today' and reaction time in the practice trial (as an indication for reaction time performance), $\rho = 0.07$, $p = 0.73$.

Table 3.3

Summary of hierarchical regression analysis predicting Attentional Bias in non-bingers.

Step	Variable	β	SE β	*p*
1	'Normal use'	0.56	0.19	0.008
2	'Normal use'	0.67	0.19	0.003
	'Drinks today'	0.06	0.19	0.760
	Time elapsed since last sip	0.38	0.19	0.059

Note N= 21. R^2=0.32 for step 1, R^2change=0.14 for step 2. Final model: R^2=0.46, p=0.014.

Table 3.4

Summary of hierarchical regression analysis predicting Attentional Bias in bingers.

Step	Variable	β	SE β	*p*
1	'Normal use'	0.29	0.21	0.175
	Gender	0.04	0.21	0.847
2	'Normal use'	0.43	0.18	0.027
	Gender	-0.21	0.19	0.278
	'Drinks today'	-0.43	0.20	0.046
	Time elapsed since last sip	0.37	0.18	0.057

Note N=24. R^2=0.09 for step 1, R^2change=0.35 for step 2. Final model: R^2=0.44, *p*=0.023.

Correlations

Urge and AB were not significantly correlated in the group of non-bingers, $r = 0.29$, $p = 0.19$, nor in the group of bingers, $r = 0.03$, $p = 0.91$. 'Drinks today', 'normal use' and BrAC were positively skewed, thus we calculated non-parametric Spearman correlation coefficients. 'Drinks today' and 'normal use' showed a positive correlation, $\rho = 0.32$, $p < 0.01$, as well as 'drinks today' and BrAC, $\rho = 0.64$, $p < 0.001$.

Discussion

In the present study, we have extended the empirical evidence on alcohol prime effects to real life settings, thereby validating results from earlier laboratory studies. Furthermore, alcohol prime effects were investigated up to much higher alcohol dose levels than in earlier studies. Results can be summarized as follows. As expected, craving ratings increased in relation to the dose of alcohol consumed, ranging from one drink (10 g of

alcohol) to 16 drinks (160 g). In addition, in line with our hypotheses, AB for alcohol-related cues decreased in relation to the amount of alcohol consumed within the subgroup of people who had been drinking in excess of a binge. Contrary to expectations however, we did not find a dose-dependent increase in AB scores in the subgroup of participants who had not binged at the time of testing.

The increase in craving ratings is consistent with a large number of laboratory studies on prime effects (see introduction). Note that the amount of alcohol ranged much higher in our study, namely up to 16 units. To compare, 0.8 g/kg has been the maximum amount in the laboratory studies that we have found, which approximates 6 Dutch units for a person weighing 75 kg.

We did not find a significant increase in AB scores in the subgroup of non-bingers, i.e. participants who had been drinking less than a binge at the time of testing. This is inconsistent with findings in our earlier study (Schoenmakers et al., 2008) and Duka and Townshend's study (2004). A difference is that in the latter studies an increase was found for a 0.3 g/kg dose of alcohol, which corresponds to approximately 2.3 Dutch units for a person weighing 75 kg. In the present study we investigated an increase up to a higher alcohol dose, i.e. three units for females, four units for males. Thus, we cannot rule out the possibility that there was an increase in the first few drinks, but soon after a decrease in this group of non-bingers. However, since there were only a few participants who had been drinking one or two drinks, we could not test the increase from one to two drinks.

The decrease in AB scores after a binge is consistent with Duka and Townshend (2004), who found lower AB after a moderate (0.6 g/kg) dose than after a low dose (0.3 g/kg) of alcohol. They explained the decrease in AB following a moderate dose of alcohol by a satiation effect. Thus, the motivation to drink would decline after a few drinks. This explanation, however, seems to contradict the available evidence of *increased* desire for alcohol in all other studies mentioned before, as well as in the present study. Social drinkers do not seem to feel satiated after a high alcohol dose (0.8 g/kg; Kirk & de Wit, 2000; Soderpalm & de Wit, 2002). We propose two possible explanations for the difference in prime effects between AB and craving, which are not mutually exclusive.

Our first explanation is that subjective, conscious feelings of craving (as measured by questionnaires) might be affected by different factors than relatively automatic reactions,

such as AB. Research has shown that stimulant and sedative effects can occur simultaneously after increased ingestion of alcohol (Earleywine & Erblich, 1996). Possibly, AB is affected by a basic affective reaction to which sedation contributes increasingly more after more alcohol, leading to a decrease in the incentive value of alcohol cues. Craving, in contrast, might be affected by more conscious processes that are biased by the positive, social context in the pub and even by asking for the urge to drink, not the urge *not* to drink. As a result, positive arousing effects might be more prominent than negative sedative effects, resulting in increased desire for alcohol. To test this idea, future studies should include measures of the urge *not* to drink (McEvoy, Stritzke, French, Lang, & Ketterman, 2004) and measures of subjective intoxication effects (Duka, Stephens, Russell, & Tasker, 1998; Earleywine & Erblich, 1996).

A second possible explanation concerns the difference between responses to alcohol cues on the one hand, and the internal stimulus properties of alcohol and the act of drinking on the other hand. An increased salience of drug-related cues (as reflected by AB) is functional in drug seeking (Robinson & Berridge, 2000), since it increases the chance of detecting the drug. When one desires an unavailable drug, drug-related cues may become sensitized (Morgan, Smith, & Roberts, 2005) and attract more attention (Field, Mogg, & Bradley, 2004a; Gross, Jarvik, & Rosenblatt, 1993), which facilitates alcohol seeking. After some drinks, subjective intoxication effects increase and it becomes evident that alcohol is easily available. Then, the saliency of alcohol cues loses its function and decreases. Concurrently, the incentive value of alcohol and reinforcing effects of drinking may still increase**.** Thus, alcohol *cues* become less determining in further alcohol use while *consuming* alcohol still determines the motivation to drink. In terms of the explanations listed by De Wit (1996): the classical conditioned effects decline while instrumental learning effects and unlearned incentive motivation increase.

There was a moderate correlation between the number of units people had been drinking on the testing day and the weekly number of units they normally drank. This suggests that on an individual level, increases in desire to drink might be restricted to a certain level where one does become satiated and stops drinking. The finding that normal alcohol use predicted craving for alcohol suggests that this level is higher for heavier than lighter drinkers, which is consistent with findings of Duka et al. (1999).

A limitation to our study is that we did not measure several variables that might have affected the desire for alcohol, AB, and drinking. The reason was that we did not want to disrupt participants' natural drinking behaviour and therefore designed a very brief procedure. Even though our measures provide sufficient evidence for the existence and course of prime effects, other measures could shed more light on underlying mechanisms and additional predictors. Future studies could, for example include measures of subjective alcohol effects to investigate the underlying mechanism for the prime effects, or incorporate information about the group in which participants were drinking (Bot, Engels, Knibbe, & Meeus, 2007).

Naturalistic drinking differs from that in lab studies in that BrAC might fluctuate during one occasion, depending on the pace of drinking and various percentages of alcohol that different types of beverages contain. Subjective intoxication effects have been found to differ between rising and falling BrAC (Earleywine & Erblich, 1996). However, we do not know the additional effect of previous BrAC fluctuation to momentary rising or falling. Future studies should address the effect of BrAC fluctuation on appetitive motivation for alcohol. Notwithstanding, we believe that our participants had a rising BrAC at the time of testing as indicated by two observations: 90 percent of our sample had taken their last sip less than 20 minutes before testing. And BrAC correlated significantly positive with the number of drinks that had been drunk at the time of testing.

With this study, we have extended knowledge from laboratory studies on alcohol priming by measuring effects up to considerably higher alcohol ingestion levels and in a real-life setting. Further, we were able to test the relationship between a wide range of alcohol ingestion levels and prime effects, instead of measuring differences on a few standardized amounts of alcohol as in laboratory studies. We showed that different aspects of appetitive motivation show a different response pattern to increased alcohol consumption. While the incentive saliency of alcohol cues decreases after a few drinks, the desire to drink keeps on increasing up to considerably high levels of intoxication. This validates earlier experimental laboratory studies and offers insides in the motivation to drink alcohol in real-life settings.

CHAPTER 4
Attention modification training in heavy drinkers: a lab study

This chapter is based on: Schoenmakers, T., Wiers, R. W., Jones, B. T., Bruce, G., & Jansen, A.T.M. (2007). Attentional re-training decreases attentional bias in heavy drinkers without generalization. *Addiction, 102*, 399-405.

Abstract

Aims To examine whether alcohol-related Attentional Bias (AB) can be reduced by training heavy drinkers to attend to soft drinks as an alternative to alcohol. Diminishing AB is important because AB has been suggested to be an important factor in the development, maintenance and relapse of addictive behaviours. AB was trained in a clinically relevant design, and we studied the generalization of this training.

Design, participants and intervention We assigned randomly 106 heavy drinking male college and university students to the attentional re-training (AR; modified visual-probe task) or control condition (standard visual-probe task).

Setting Laboratory at Maastricht University.

Measurements We measured the effects of AR on the visual-probe task with stimuli that were presented in the AR and with new stimuli, and on an alternative measure of AB, the flicker paradigm. We further measured effects on craving and preference for either an alcohol beverage or a soft drink.

Findings After AR, participants had learned to avoid alcohol stimuli and had developed an AB for soft drinks. This effect was restricted to stimuli used in the AR. The flicker task, where AB for alcohol was found in both the AR and control groups, was not affected by the AR. No effect was found on craving and the preference task.

Conclusions Although heavy drinkers can learn to attend selectively to an alternative category for alcohol, a single AR is not sufficient to decrease symptoms of problem drinking.

It has been hypothesized that attentional bias (AB) for alcohol or drug-related stimuli elicits craving and drug seeking behaviour (Franken, 2003; Lubman, Peters, Mogg, Bradley, & Deakin, 2000), leading to the development, maintenance and relapse of addictive behaviours (Cox, Fadardi, & Pothos, 2006; Cox, Hogan, Kristian, & Race, 2002; Franken, 2003). Attention prioritizes detection, selection and monitoring of certain stimuli over others and as such has been proposed to mediate cognition, emotion and behaviour (Cox, Fadardi, & Klinger, 2006). AB is a particular readiness to process certain stimuli rather than others, triggered by the incentive value of appetitive stimuli (Robinson & Berridge, 1993, 2001). This process instigates corresponding cognitions (Sayette, 1999), that cause attention either to maintain the selected stimulus or to avoid it (Mogg, Bradley, De Bono, & Painter, 1997). Avoidance from alcohol stimuli has been found in inpatient alcoholics (Stormark, Field, Hugdahl, & Horowitz, 1997), probably because they are aware of negative consequences, and have negative implicit associations with alcohol (Wiers, Houben, Smulders, Conrod, & Jones, 2006).

The aims of the present study are to test a training method to reduce attentional bias (attentional re-training, or AR[6]) in heavy drinkers and to measure subsequent effects on craving and behaviour. Our re-training is based on a standard AB measure, the visual-probe task. Two other AB measures often used in alcohol research are the flicker paradigm for induced change blindness, and the addiction-Stroop task. Results of the addiction-Stroop task, however, are difficult to interpret (Cox, Fadardi, & Pothos, 2006). We have selected the visual-probe and flicker paradigm as dependent measures in this study. In the visual-probe task, two stimuli representing two categories (e.g. alcohol and neutral) are presented simultaneously on a computer monitor. After a short interval the stimuli disappear, and a probe consisting of one or two pixels replaces one of the stimuli. Participants differentiate as quickly as possible between the probes by pushing one of two buttons. Faster responses to probes replacing alcohol stimuli indicate AB towards alcohol relative to neutral stimuli. AB in heavy drinkers has been found with stimulus presentations of 500 ms (Field, Mogg, Zetteler, & Bradley, 2004; Townshend & Duka, 2001) and 2,000 ms (Field, Mogg, Zetteler et al., 2004). In the flicker paradigm, a display with alcohol-related and neutral objects is

[6] In Chapters 1 and 6, this training is referred to as 'avoid-attention modification training' (avoid-AMT)

presented for 250 ms on a computer screen. A mask is then presented for 80 ms, followed by the display with one object changed and again the mask. This sequence is repeated until participants detect the change. Jones et al. (B. T. Jones, Jones, Smith, & Copley, 2003) found that heavy, but not light, drinkers detected alcohol-related changes faster than neutral changes.

AB has been found to correlate with craving for alcohol (Field, Mogg, & Bradley, 2006; Franken, 2003). Until recently, however, the causal direction of this relationship had not been demonstrated experimentally. The best way to test whether AB causes craving is to manipulate AB and examine the effect on craving (see Mathews & MacLeod, 2002). Note, however, that this leaves open the possibility that the relationship is bidirectional (Franken, 2003).

Recently, researchers investigated the possibility that heavy drinkers' AB can be manipulated by using modified AB measures (Wiers, Cox et al., 2006). The idea stems from MacLeod et al.'s pioneering work in anxiety research (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mathews & MacLeod, 2002). They demonstrated a causal effect of AB for negative stimuli on emotional vulnerability. In their 'attention training', participants were subjected to a modified visual-probe task with threatening and neutral words. In a standard visual-probe task, probes are distributed on a 50/50 basis over both categories over multiple trials. In the training version, however, probes mostly replaced threatening words for the 'attend-negative' group and neutral words for the 'attend-neutral' group. Results showed that during the training, the attend-negative group had learned to selectively attend to threatening stimuli and showed more negative reactions to a subsequent stress task than the attend-neutral group.

Field and Eastwood (2005) demonstrated that AB for alcohol has a causal effect on craving and drinking behaviour. They used a modified visual-probe task (MacLeod et al., 2002) to train half of their heavy drinking participants to attend to alcohol pictures and the other half to avoid alcohol pictures (AR). Participants in the attend-alcohol condition demonstrated increased AB from pre- to post-attention-training, and these participants reported more craving (measured on a one-item scale) and drank more beer in a post-training taste test than participants in the attend neutral group, With this design, however, it is not possible to determine whether differences in craving and drinking behaviour are

caused by an increase in one group, a decrease in the other group, or both. The same accounts for the depression measures in MacLeod et al.'s study (2002). Our study has been designed to overcome this problem by using a control group that was not trained, but performed a prolonged version of the standard visual-probe task.

In anxiety research, reductions in symptoms of psychopathology have been reported after multiple AR sessions to diminish AB (see De Jong, Kindt, & Roefs, 2006). The purpose of the present study was to test possibilities and impact of AR on addictive behaviours. It is the first study to test experimentally a clinically relevant AR in addiction in a large sample of problem drinkers. Our design differs from Field and Eastwood's in two aspects. First, we tried to assess AR-effects by comparing participants who were trained to avoid alcohol pictures with a control group that performed a prolonged visual-probe task instead; in this way, we could determine the effectiveness of treatment compared to no-treatment. Second, instead of neutral pictures we trained participants towards soft drinks, a relevant alternative for alcohol (Houben & Wiers, 2006; Wiers, Van de Luitgaarden, Van den Wildenberg, & Smulders, 2005; Wiers, Van Woerden, Smulders, & De Jong, 2002).

Rather than learning to avoid the specific stimuli used in the AR, problem drinkers should eventually learn to avoid alcohol in general. Therefore, our post-AR-test visual-probe measured not only effects with stimuli from the AR, but also with new stimuli. In anxiety research, effects on new stimuli have been found (MacLeod et al., 2002; Yiend & Mackintosh, 2004), but in alcohol research generalization has not yet been explored. A second unattended generalization issue we address is whether the AR-effect generalizes to an alternative AB measure, the flicker paradigm (B. T. Jones, Jones, Smith et al., 2003). AB measures, however, correlate poorly (Mogg & Bradley, 2002; Mogg et al., 2000) and therefore their results might not necessarily correspond. We also investigated effects of AR on craving and preference for an alcoholic or a soft drink.

To summarize, our first hypothesis was that AR would result in a diminished AB for alcohol in the AR group, compared with the control group. Secondly, we explored whether this difference would be found for new stimuli. Thirdly, we explored whether we could measure a corresponding difference with the flicker paradigm. Fourthly, we hypothesized that, after AR, participants would choose a soft drink more readily than an alcohol

beverage, compared with the controls. Fifthly, we hypothesized that the AR group would crave less for alcohol than the control group after AR.

Method

Participants

Participants were 106 male undergraduate students from Maastricht University and a nearby vocational college. They were selected for drinking heavily (> 20 Dutch standard drinking units of 10 g of alcohol per week), measured with a self-report questionnaire (Wiers, Hoogeveen, Sergeant, & Gunning, 1997) based on the time-line follow-back procedure (Sobell & Sobell, 1990). We selected them also on having had at least one binge-drink episode in the last 2 weeks prior to selection. Mean age was 21.4 years (SD = 2.0). On the Rutgers Alcohol Problems Index (White & Labouvie, 1989, 2000), participants scored 19.35 (range: 3 - 36), an average item score of 1.07; 72 % scored above the average of clinical samples, 0.80 (White & Labouvie, 1989). On the Alcohol Use Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993), participants scored 14.40 on average (range 7-25); 91 % scored above 10, the cut-off score for alcohol problems (Saunders et al., 1993); 98 % scored above eight, indicating hazardous drinking (Palfai & Ostafin, 2003). Participants were assigned randomly to either the AR or control condition (N = 53 per condition). On average, AR participants drank 40 standard Dutch units per week (range 21 - 94), as did control participants (range 21 - 87). Groups did not differ on age, alcohol use, and alcohol problems (all *p*s > 0.70).

Materials

We used 30 alcohol-related pictures for the AR and pre- and post-test visual-probe. Each of these pictures was paired with a soft drink picture, matched by colour, height, width and shape (Figure 4.1), following Jones and colleagues (B. T. Jones, Bruce, Livingstone, & Reed, 2006). Some of these pairs were used in pre-test, AR and post-test, some in AR only, and some in the post-test only. Height was standardized to 9 cm. We used another 11 alcohol-

related pictures for the flicker paradigm and matched those with 11 soft drink pictures. Both tasks were programmed in ERTS 3.18 (Beringer, 1996).

Figure 4.1

Example of a matched picture pair (left alcohol, right soft drink) as used in the visual-probe task.

Procedure

Participants were recruited by e-mail briefings and posters and flyers in university buildings and fraternities. In a telephone interview, we screened their drinking behaviour. On the test day, prior to inclusion in the study, they gave informed consent. They were then tested in separate cubicles containing a computer.

First, participants were primed with a sip of beer (all participants were regular beer drinkers) because this may increase the chance of finding AB in heavy drinkers (Cox, Brown, & Rowlands, 2003; Duka & Townshend, 2004; B. T. Jones & Schulze, 2000). They then rated their craving for alcohol and performed the pre-test visual-probe. Subsequently, AR started for the experimental group and a prolonged standard visual-probe task for the control group, followed by the post-test visual-probe and the flicker task. Finally, all participants could choose a free alcohol or soft drink (preference task), after which we measured successively craving for alcohol and problem drinking. At the very end,

participants were asked about their ideas concerning the purpose the study (awareness check). After all participants were tested, they were debriefed by email about the real purpose of the study. They received 11 euros for participating.

Visual-probe and AR

The visual-probe task consisted of three consecutive phases: a pre-test, the AR or control phase, and a post-test. In all phases, trials consisted of a picture representing alcohol and one representing soft drinks. The tests were identical for both groups. They consisted of 48 trials, with a 50/50 distribution of probes over the two categories: probes replaced both alcohol and soft drinks in 24 trials. The pre-test consisted of 12 different picture pairs, which were repeated four times. The post-test presented six 'old' picture pairs that were used in the AR phase, and six 'new' picture pairs that had not been used previously.

The AR phase consisted of 624 trials, following MacLeod et al. (2002). Probes replaced soft drinks in 600 trials and alcohol in 24 trials. Two sets of picture pairs were used, each with a different probe distribution, together constituting a 96/4 distribution. The first set was used for 576 critical trials with a 100/0 (soft drinks/alcohol) probe distribution. This set consisted of 24 different picture pairs, each repeated 24 times; half of these 24 picture pairs had been used in the pre-test, and half were new. The second set was used for 48 filler trials with a probe distribution of 50/50. This set consisted of 12 different picture pairs (six from the first set, and six new pairs), each repeated four times. The filler trials were spread randomly throughout the AR phase. The control phase differed from the AR phase only in the probe distribution: control participants were presented with the same picture pairs as often as the AR participants, only the probe distribution was 50/50 in all 624 trials.

Pictures were presented on a grey background on a computer screen, with an average distance of 6 cm between their inner angles. Trials began with a fixation cross in the middle of the screen. A picture pair was then presented for 500 ms and replaced by a probe that randomly, with a 50 % probability, consisted of one or two white pixels. Participants were to respond as quickly as possible: pushing one button if the probe consisted of one pixel and another button for two pixels. Feedback was given in case of a response that was too slow (> 3,000 ms), too fast (< 150 ms) or wrong (wrong button). After a correct response, the

screen was cleared for 500 ms after which the next trial started. Participants were seated at approximately 60 cm from the screen.

Flicker paradigm

Participants performed four flicker trials, each consisting of the presentation of a 3 x 6 matrix of alcohol and soft drink pictures with nine alcohol pictures on one side (3 x 3) and nine soft drink pictures on the other side (3 x 3). Matched alcohol-soft drink pairs were placed on the opposite side of the matrix, mirrored against the vertical middle line. Trials started with 250 ms presentation of the original matrix, followed by 80 ms presentation of a mask. Then 250 ms presentation of the matrix with one picture being replaced by another, followed by 80 ms presentation of the mask. This loop was repeated until the participant noticed the change and pressed a button corresponding to the side of the change, left or right. The dependent variable was response latency. In random order, each participant was given two alcohol and two soft drink changes. Changes were in the middle line of the 6 x 3 matrix, each on a different position. For every individual, alcohol and soft drinks were presented on the same side of the screen in all trials, sides being balanced within groups.

Preference task

Preference for alcohol or soft drinks was measured by offering participants a choice between four different, well-known drinks (see Karpinski & Hilton, 2001). Participants were individually presented with a serving tray containing two cans of beer and two cans of soft drink, colour-matched. They could choose one can to take home with them.

Craving for alcohol

Participants indicated their urge to drink alcohol 'right now' on a single analogue scale (Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996) of 100 mm, ranging from 'no urge at all' to 'an almost irresistible urge'.

Results

Visual-probe task

Following MacLeod et al. (2002), we calculated median discrimination latencies to minimize the effect of outliers. Latencies under 200 ms and over 2,000 ms were excluded from analyses; data from error trials were also excluded (totaling 3.6 % of data in pre-test, 4.8 % in the post-test). We calculated AB scores by subtracting latencies on congruent trials (alcohol) from latencies on incongruent trials (soft drinks); a positive score indicating AB for alcohol, a negative score AB for soft drinks (Table 4.1).

Our main hypothesis was confirmed by a 2 x 2 mixed design analysis of variance (ANOVA), with condition (AR/control) as the between-subjects factor, and time (pre-test/post-test visual-probe) as the within-subjects factor. The ANOVA revealed a significant interaction effect in the predicted direction: $F(1, 104) = 4.73$, $p < 0.05$). Independent-samples t-tests indicated that groups did not differ on AB scores on the pre-test, $t(104) = 0.84$, $p = 0.40$. However, in the post-test AR participants had a significantly smaller AB score than control participants, $t(104) = -2.38$, $p < 0.05$, indicating that AR had been effective in diminishing attention for alcohol relative to soft drinks.

To explore whether the AR-effect had generalized to new pictures, we compared AB scores on new pictures between the groups. An independent samples t-test revealed no significant difference: $t(104) = -0.63$, $p = 0.53$; AR had not significantly changed AB measured with new pictures.

Table 4.1

Averaged median response latencies and AB score in visual-probe task for AR group and control group.

		AR (N = 53)		Control (N = 53)	
		Median	SD	Median	SD
Pre-test	Alcohol	641.09	98.00	652.59	86.12
	Soft drinks	646.68	80.61	648.43	96.17
	AB	5.59	69.11	-4.15	48.39
Post-test	Alcohol	578.01	58.76	569.27	64.18
	Soft drinks	564.70	59.50	577.18	67.49
	AB	-13.32	51.34	7.91	39.86
	Alcohol old	582.84	75.43	567.09	78.65
	Soft drinks old	560.55	67.52	574.54	66.81
	AB old	-22.29	75.68	7.45	70.12
	Alcohol new	577.64	64.81	571.24	67.09
	Soft drinks new	569.16	72.12	571.39	77.13
	AB new	-8.48	66.53	0.15	73.77

Note AB = attentional bias; AR = attentional re-training; median = Averaged median scores per group (in ms); SD = standard deviation from averaged median scores.

Flicker paradigm

One outlier with a mean AB score of more than two standard deviations from the group mean was excluded from analyses. Data from one participant were lost because of technical problems. Both were control participants. We calculated the flicker scores by averaging latencies for each category. To explore whether the AR-effect had generalized to the flicker paradigm, we performed a 2 x 2 ANOVA with condition (AR/control) and stimulus type (alcohol/soft drinks) as independent variables. The interaction was non-significant, $F(1, 102) = 0.27$, $p = 0.60$, indicating no generalization. We found no correlation between the flicker and the post visual-probe task ($R = -0.10$, $p = 0.31$), possibly explaining this finding. The main effect for stimulus type in the ANOVA was significant, $F(1, 102) = 5.03$, $p < 0.05$, showing a shorter overall alcohol latency ($M = 4802$ ms, $SD = 3385$ ms) than soft drinks latency ($M = 5812$ ms, $SD = 3733$ ms), indicating AB for alcohol irrespective of group.

Preference task

One participant in the AR group refused a can. Of the remaining 52 participants in the AR group, 34 (65 %) chose an alcoholic beverage, compared with 29 out of 53 (55 %) in the control group. A Chi-Square test revealed no significant difference, $X^2(1) = 1.25$, $p = 0.27$.

Craving for alcohol

To test whether the AR would decrease urge to drink alcohol, we performed a mixed 2 x 2 ANOVA with group (AR/control) as the between subjects factor and time (urge before AR/after AR) as within subjects factor (Table 4.2). No significant interaction was found, $F(1, 104) = 0.22$, $p = 0.64$; AR had not affected craving.

Awareness check

Six participants in the AR condition and eight in the control condition recognized that focus of attention was measured with the visual-probe task. Analyses of visual-probe scores were repeated without these participants, but results did not change. None of the participants recognized correctly the purpose of the AR.

Table 4.2

Craving for alcohol for AR group and control group.

	AR		control	
	M	SD	M	SD
Before AR	38.08	22.70	32.85	26.41
After AR	42.15	25.30	35.36	27.05

Note Scores are measured on a single analogue scale, possible range of scores 0 mm (no urge at all) to 100 mm (an almost irresistible urge). AR = attentional re-training; M = mean; SD = standard deviation.

Discussion

AR was successful in decreasing attention for alcohol stimuli relative to the alternative category, soft drinks. This conclusion should, however, be qualified: the change in AB was not significant for pictures that were not used in the AR. Further, the AR and control group did not score differently on the flicker paradigm, suggesting lack of generalization outside the task that was used to retrain. Additionally, AR did not decrease craving and preference for alcohol.

Although AB scores on new pictures were smaller for the re-training group than for the control group, this difference did not reach statistical significance. MacLeod et al. (2002) did find generalization effects to new stimuli. This might be explained by differences in experimental designs; MacLeod et al. trained one group towards, and the other away from threatening stimuli, thereby creating a bigger difference between AB scores of both experimental groups than found in our study (see Figure 2 in Wiers, Cox et al., 2006); this increases the chance of finding an effect. Such a watershed design contrasts with our clinically relevant design: we only trained one group; the control group was not trained.

Another difference in design that may account for our limited generalization to new stimuli concerns the number of picture pairs in the re-training. In the training of Macleod et al. (2002), 48 word pairs were repeated 12 times, while in our AR 12 picture pairs were repeated 48 times. Hence, MacLeod et al. trained more different exemplars of one category. Their large number of stimuli might have better represented a full category. Our specific stimuli might not have been sufficient to represent a full category. Thus, to find a stronger generalization effect, it could be useful to use more different stimuli in the re-training.

Furthermore, instead of words, pictures are often used as stimuli in AB tasks, because they are more naturalistic and ecologically valid (Lubman et al., 2000). At the same time, this renders them more specific. This specificity weakens the relation between the AB task and craving and drinking behaviour if pictures are chosen that do not represent drinks that participants normally drink. In this sense, personalizing the stimuli could be a useful option (Fadardi, Cox, & Klinger, 2006).

Alternatively, incongruent findings regarding effects of AR may depend on different mechanisms underlying AB in different domains, addiction and anxiety. In addicted and anxious individuals, attention is directed towards appetitive and threatening stimuli, respectively. Anxiety AB has been theorized to be caused by a vigilance-avoidance pattern to reduce subjective discomfort (Mogg & Bradley, 1998) while AB towards drug stimuli has been hypothesized to result from maintenance of attention or a disengagement problem (Field, Mogg, Zetteler et al., 2004; Stormark et al., 1997). It is thought that different neural systems may underlie AB in the different domains (Field, Mogg et al., 2006). Therefore, it is necessary to be careful with generalizations concerning mechanisms of AR and AB across domains. In fact, one has to consider the possibility that AR in addiction might not work as well as in anxiety or that it may work more effectively using another task (Wiers, Cox et al., 2006).

The results of the present study replicated and extended Field and Eastwood's (2005) findings regarding AR in alcohol abuse. Both studies found a change in their measure of AB (visual-probe task). Additionally, we found that this effect showed no significant generalization to new stimuli within the visual-probe task, which was not investigated by Field and Eastwood. Another extension in our study was the measurement of the AR-effect with an alternative AB task. Two possible reasons may account for the finding that the AR-

effect did not generalize to the flicker paradigm. The first is that the pictures in the flicker paradigm were different from the ones used in the AR. Because the effect with new pictures in the visual-probe was limited, it might be expected to be even smaller in another task. The second reason concerns poor correspondence between the two AB measures. We found no significant correlation between the flicker paradigm and post-test visual-probe, due perhaps to a low reliability of the tasks (Cunningham, Preacher, & Banaji, 2001; Payne, Cheng, Govorun, & Stewart, 2005). A critical difference between the measures could be the response target. In the visual-probe task participants respond to a probe, whereas in the flicker paradigm participants respond to a stimulus.

Field and Eastwood (2005) found an increase in craving after participants were trained to attend to alcohol pictures, demonstrating a causal effect of AB on craving. We did not find support for this causality, as the decrease in AB did not diminish craving. This finding is consistent with results for the avoid alcohol group in Field and Eastwood's study; craving for participants who had learned to avoid alcohol did not decrease after a decrease in AB. However, in our study, the AR-effect on craving might have disappeared because of exposure to alcohol cues in the preference task.

We address some limitations to our study to help improve future investigations of AR. First, we trained participants only once. In the paper by Wiers, Cox et al. (2006), Fadardi and Cox describe that they have retrained participants' AB for alcohol and measured a decrease in drinking after multiple AR sessions (using a modified Stroop task as AR). Additionally, descriptions of studies on reducing AB as a treatment for psychopathologies (general anxiety disorder; social phobia) report effects on other measures (apart from AB itself) only after multiple sessions (De Jong et al., 2006; Yiend, 2004). Studies that did find a strong effect after one session aimed at increasing AB (Field & Eastwood, 2005; MacLeod et al., 2002); decreasing AB to reduce psychopathology seems to require more effort. Secondly, we recommend using 'old' pictures in the alternative AB task as well. That way, one can differentiate generalization to the alternative task from generalization to new stimuli. Thirdly, we measured behaviour indirectly with a preference task. We did not measure drinking behaviour directly with, for example, a taste-test, because of our primary interest in generalizability of AR. Finally, we have included only males in our study. Possibly, women react differently to AR.

In summary, the main purposes of this study were to explore possibilities of AR as a clinical tool and to test AR for its generalization properties. To our knowledge, this is the first study in which a clinically designed visual-probe re-training has been tested experimentally in a large sample of problem drinkers. We found that it is possible to train problem drinkers to attend selectively to an alternative category for alcohol. However, this effect was only significant for specific stimuli that were presented in the re-training and did not impact behaviour. Thus, the single re-training did not reveal clinically relevant effects. We believe that multiple AR sessions with more different (new) stimuli should be applied to test whether AR is capable of reducing craving and subsequent drinking behaviour in a clinically relevant way.

CHAPTER 5
Attention modification training in alcohol dependent patients: an RCT

This chapter is based on: Schoenmakers, T., De Bruin, M., Lux, I. F. M., Goertz, A. G., Van Kerkhof, D. H. A. T., & Wiers, R. W. (under review). Attentional Re-training in Alcohol Dependent Patients: a randomized controlled trial.

Abstract

Attentional bias for disorder-related stimuli underlies different forms of psychopathology. In alcohol dependency, attentional bias is associated with severity of alcoholism, craving, treatment outcome, and relapse. In this study, a training to decrease attentional bias (Attentional Re-training, AR) was tested as an addition to cognitive behavioural therapy for alcohol dependent patients. In 3 treatment centers, 43 patients with DSM-IV diagnosis of alcohol dependence were randomly assigned to an AR intervention or control training. The AR intervention consisted of 5 sessions in which participants were trained to disengage attention from alcohol-related stimuli. AR was effective in increasing the ability to disengage from alcohol-related cues, which generalized to untrained stimuli. There were no significant effects on subjective craving. After the intervention, in the clinic with the shortest regular treatment program, AR participants were sooner discharged than control participants. Among the patients who (re)lapsed after the intervention, time to (re)lapse was longer in the AR condition. Results of the study suggest that AR might be valuable addition to the treatment of alcoholism and might stimulate AR research in other areas of psychopathology.

There is accumulating evidence that involuntary or uncontrolled cognitive mechanisms play an important role in psychopathology (Mobini & Grant, 2007; Wiers, Teachman, & De Houwer, 2007). Current cognitive behavioural treatment programs primarily target voluntary information processing, which may leave disadvantageous involuntary processes intact (McNally, 1995; Öhman, 1996). Therefore, new interventions are being developed that aim to directly target these processes.

In drug addiction, a central and much researched involuntary cognitive process is attentional bias (AB). This is an uncontrolled selective attention for drug cues, mediated by dopaminergic mechanisms (Robinson & Berridge, 1993; Volkow, Fowler, Wang, Swanson, & Telang, 2007), which is assumed to have causal effects on substance abuse, addiction development and maintenance (Field & Eastwood, 2005; Franken, 2003; Weinstein & Cox, 2006). AB has been studied in addiction for alcohol (Field & Cox, 2008; B. T. Jones, Bruce, Livingstone, & Reed, 2006; Stetter, Ackermann, Bizer, Straube, & Mann, 1995) and illicit drugs, including heroine (Lubman, Peters, Mogg, Bradley, & Deakin, 2000) and cocaine (Vadhan et al., 2007). It is related to addiction in different ways. First, AB is theorized to share a reciprocal causal relationship with craving (Franken, 2003; Robinson & Berridge, 1993), although this relationship is not evident in all circumstances (Lubman et al., 2000; Noël et al., 2006; Waters et al., 2003). Further, studies have shown associations between AB and the severity of addiction (Bearre, Sturt, Bruce, & Jones, 2007; Fadardi & Cox, 2006; B. T. Jones et al., 2006; Noël et al., 2006), poor treatment (Carpenter, Schreiber, Church, & McDowell, 2006), and relapse following treatment (Cox, Hogan, Kristian, & Race, 2002; Marissen et al., 2006; Waters et al., 2003). Correspondingly, excessive drinkers with low compared to high AB have been found to be three times more successful in cutting down (Cox, Pothos, & Hosier, 2007). Altogether, an intervention that decreases addicts' AB might positively influence their recovery.

Macleod and colleagues (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002) developed a computerized task to directly modify AB for negative stimuli in anxiety (see also Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007; Fadardi & Cox, 2007). It can modify fast attention processes, such as the speeded detection of disorder-related stimuli (words or pictures), and slower attentional processes, such as the difficulty to disengage from these stimuli. Typically, effects of attention training are measured on AB

for new stimuli that have not been used in the training (generalization), and on other disorder relevant cognitions and behaviours. So far, this training has been tested only in non-clinical samples in anxiety (MacLeod et al., 2002; MacLeod, Soong, Rutherford, & Campbell, 2007; Mathews & MacLeod, 2002) and alcohol misuse (Field, Duka et al., 2007; Field & Eastwood, 2005; Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007). The present study tests a training to decrease AB (i.e. attentional re-training, AR[7]) in a clinical population of alcohol dependent patients.

Effects of alcohol-AR in non-clinical samples have been rather weak, i.e. no generalization toward novel stimuli and no decrease in craving or drinking behaviour (Field, Duka et al., 2007; Field & Eastwood, 2005; Schoenmakers et al., 2007). Reviewing the literature on attention modification paradigms, three aspects seem to increase the effectiveness of trainings and were therefore employed in the present study. The first is to motivate participants to improve training performance and control over their attention (Fadardi & Cox, 2007). The second is presenting a large number of different stimuli in the training, since generalization toward new stimuli has only been found after trainings with more stimuli than used in previous alcohol-ARs (MacLeod et al., 2002; MacLeod et al., 2007; Smith, Dip Sci, & Rieger, 2006). The final aspect is performing multiple training sessions; single ARs affected only state vulnerability for stress (MacLeod et al., 2002), whereas repeated AR sessions affected trait anxiety (Mathews & MacLeod, 2002). In addition, effects on fast attention processes were found after multiple sessions (Mathews & MacLeod, 2002), but not after a single session (MacLeod et al., 2002).

The goal of the present randomized controlled trial was to train alcoholic patients' ability to control their attention for alcohol cues. We modified our earlier AR paradigm (Schoenmakers et al., 2007) based on the three aspects reviewed above: motivation, many stimuli, repeated sessions. Compared to a control task, we expected the AR to decrease speeded detection of old and new alcohol stimuli and decrease the difficulty to disengage from those stimuli. Additionally, we tested effects of the AR on craving, lapse, relapse and overall treatment success.

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[7] In Chapters 1 and 6, this training is referred to as 'avoid-attention modification training' (avoid-AMT).

Method

Participants

Participants were 33 male and 10 female alcohol dependent patients from three treatment centers in the Netherlands who all received cognitive behavioural therapy. Prior to data collection, a power analysis based on earlier, single session alcohol AR studies determined that a sample size of 52 was needed to detect large differences between groups after the intervention. However, due to time restraints and low admission rate in the clinics a sample size of 43 was achieved. All 43 participants were Caucasian and had the Dutch nationality. The sample consisted of 33 inpatients (Heerlen: n = 23; Arnhem: n = 10) and 10 outpatients (Maastricht). The regular treatment program was approximately three months in Heerlen, and six months in the other centers. To be included in the study, patients had to be in treatment for no longer than two months, and had to meet DSM-IV criteria for alcohol dependence. They were excluded when they received anti-craving medication during the intervention, when alcohol was not their main addiction and when they were diagnosed for mental disorders other than drug or alcohol dependence. Patients who lapsed during the intervention, as reported by a patient or therapist, were dismissed from the study.

At the start of the first training session, participants were randomly assigned to the AR or control group, stratified by gender and treatment center. Beforehand, a randomization sequence was generated by www.randomization.com and used for each stratum. Only the experimenter had access to this sequence. To ensure an equal distribution of assignments to the AR and control group, the maximum number of consecutive assignments to one group in this sequence was restricted to three. Groups did not differ on baseline demographic and clinical characteristics (Table 5.1).

Materials

We used the picture set from our earlier study (Schoenmakers et al., 2007) and added another 30 pictures. Alcohol pictures consisted of different kinds of alcohol beverages and objects, neutral pictures consisted of soft-drinks, furniture or stationery. Five sets of twelve matched alcohol–neutral picture pairs were created. Set 1 was used in both visual-probe

tests. Sets 1 to 4 were used in different combinations in the AR/control tasks. Set 5 ('new pictures') was used in the visual-probe post-test. Eight 'neutral–neutral' pairs were created for practice and filler trials. Tasks were programmed in ERTS 3.18 (Beringer, 1996).

Table 5.1

Demographic and Clinical Characteristics per Group

	Attentional re-training N = 21		Control N = 22	
Variable	M	SD	M	SD
Age at entry (years)	44.19	9.42	45.82	10.28
Alcohol use per day before treatment	24.57	13.13	28.77	22.92
Period of alcoholism (years)	10.00	8.99	6.86	8.84
Number of prior detoxification treatments	1.95	2.27	1.18	0.39
Cigarettes per day	19.15	14.64	20.10	12.90
Education	3.62	1.24	4.00	1.38

Note Alcohol use is in Dutch standard units of 10 g of alcohol. Education is based on a standardized classification system (Statistics Netherlands, 2006) ranging from 1 (no education) to 7 (post-doctoral education).

Procedure

Patients were informed by their therapist about the possibility to participate in a research project on re-training of attention for alcohol. They were explained that addiction is partly maintained by uncontrolled distraction by alcohol-related objects. Since motivation was an important aspect of the training, and motivation would be low in patients suspecting to be in the control group, they were told that the study would test the effectiveness of two training programs to increase control over distraction by alcohol. Patients and therapists

were blind for training condition and therapists were instructed not to discuss the training with their patients. Before commencing with the intervention, written informed consent was obtained. These procedures were approved by the Medical Ethical Committee of the Clinical Trial Center Maastricht, The Netherlands. All recruitment, testing and follow-up data collection took place between July 2006 and September 2007.

The intervention consisted of five training sessions and a post-test session, every Monday and Thursday or Tuesday and Friday at a fixed time. All sessions took place in a quiet room inside the treatment centers. In session 1, after measuring patients' demographics, craving was measured. Identical general instructions were given for the training and control task: the training was meant to increase control over shifting and focus of attention and that reaction times (RTs) in the tasks would reflect participants' ability in doing so. Therefore, the general goal was to decrease RTs during the course of the training program. Participants then performed their first AR/control task. Next, they were given positively framed feedback on their mean RT and performance accuracy. Together, the experimenter and participant set up a goal for the next session based on the average RT and accuracy. Typically, the goal was to decrease overall RT with 20 ms and increase or stabilize accuracy up to 95 %. Finally, patients were interviewed about their alcohol consumption before treatment with the Composite International Diagnostic Interview 2.1 (Robins et al., 1988) and the first part of Section III of the EuropASI (Kokkevi & Hartgers, 1995).

Sessions 2 to 5 started with recapitulation of the goals formulated during the previous session, followed by the AR/control task. Each session ended with positive feedback on performance and new goals for the next session. In the post-test session, participants first filled out the DAQ and then performed the visual-probe post-test. Participants received 30 euros for participating.

Visual-probe Task

Each trial of the visual-probe task (Bradley, Mogg, Falla, & Hamilton, 1998) started with a fixation cross for 500 ms. Then, two pictures were simultaneously presented left and right from the centre of the screen. This was done for 200 ms (measuring speeded detection of

alcohol-related stimuli) or 500 ms (measuring the difficulty to disengage from alcohol-related stimuli). Immediately after picture offset, an arrow, pointing up or down with a 50 % probability, replaced one of the two pictures. Participants were instructed to look at the fixation cross at the start of each trial, and to classify the probe as fast as possible by pressing the corresponding upper or lower button on a response box. There was a variable intertrial interval between 500 and 1000 ms.

The pre-test (session 1) started with 16 practice trials. Instructions were then clarified followed by four buffer trials and 48 critical trials with 16 filler trials randomly interspersed. After a short break and again four buffer trials, a remaining 48 critical trial and 16 filler trials were performed. In the critical trials, twelve picture pairs were each repeated eight times. Half of the time picture pairs were presented for 200 ms and half of the time for 500 ms. For each stimulus duration, probes replaced the alcohol picture and neutral picture equally often, and each picture type was equally often located left or right from the centre of the screen. The procedure of the post-test was identical to the pre-test, except for that it did not include practice trials. Additionally, the task consisted of 24 picture pairs (twelve old pairs from the training program, twelve new ones), each repeated four times.

Attentional Re-training and Control Task

The intervention consisted of five AR or control tasks. The AR task was a modified visual-probe task. It consisted of alcohol – neutral picture pairs only, and probes replaced the neutral picture in all trials. Half of the time picture pairs were presented for 200 ms (to decrease fast attentional engagement toward alcohol cues) and half of the time for 500 ms (to decrease the difficulty to disengage from alcohol cues). A task consisted of 24 picture pairs that were repeated 22 times over seven blocks. Odd blocks consisted of 96 trials with alcohol – neutral picture pairs. To make the task more challenging, the even blocks were composed of 48 trials with three instead of two simultaneously presented pictures: two identical alcohol pictures and one neutral picture, positioned in an isosceles triangle shape. Pictures were equally divided over the three locations. Before each AR task, participants were told that probes would never replace the alcohol-related picture. Since this instruction could interfere with the visual-probe post-test, prior to that test it was stressed that it was

not a re-training, and probes would replace the alcohol and non-alcohol picture equally often.

The control task allowed us to give the same type of feedback, set similar goals, and to show the same pictures as in the AR task, without influencing AB. The control task was a categorization task, similar in design as the Implicit Association Task (Greenwald, McGhee, & Schwartz, 1998). In each trial of the control task, a target stimulus appeared in the centre of the screen. Participants had to press left or right to classify the target as alcohol-related or non-alcohol-related (neutral), a number or a colour name. A task consisted of five consecutive phases that were repeated twice; a colour - number discrimination phase, an alcohol - non-alcohol discrimination phase, a combination phase (with all four categories), a reversed alcohol - non-alcohol discrimination phase, and a reversed combination phase. Discrimination phases consisted of 24 trials, combination phases consisted of 48 trials.

After each block in visual-probe task and after each combination phase in the control task, participants got a computerized report stating the mean RT and accuracy (percentage of correct responses) in that particular block or phase.

Craving

We measured craving with the 14 item Desires for Alcohol Questionnaire (Love, James, & Willner, 1998), which consists of four factors: mild desires, strong desires, perceived control over drinking, and reinforcement expectancies. All items range from 1 ('strongly disagree') to 7 ('strongly agree').

Follow-up

Three months after the last session, participants who had completed the intervention were sent a follow up questionnaire about their treatment status and alcohol use in the past three months. Additionally, medical files of patients were consulted for the same variables. Time to lapse was defined as the first time drinking one alcoholic beverage, time to relapse as the first time drinking at least six glasses on one occasion.

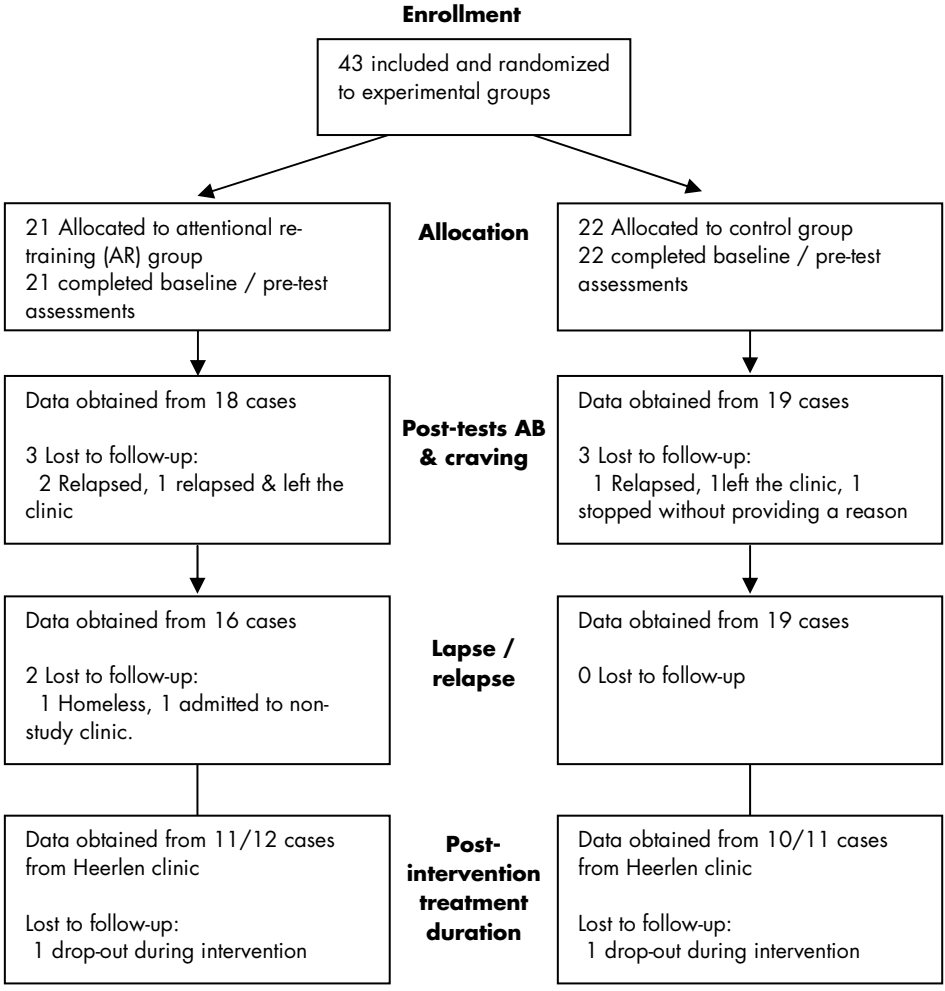
Data Analyses

Attrition

Of the 43 participants that were initially included, 37 completed the intervention and post-test measures. Six patients dropped out of the intervention; three of those relapsed during the intervention (two from the AR group, one control), one (control) stopped without providing a reason, two (one AR, one control) left the clinic against therapists' advice. These six patients did not differ from the other patients at baseline / pre-test measures.

Of the 37 patients who had completed the intervention, we gathered lapse and relapse data of 35 patients; thirty-one patients (15 AR, 16 control) returned the questionnaire, data from another four patients (one AR, three control) could be retrieved from their medical files. One patients was lost to follow-up (AR) and one (AR) had been admitted to another non-study clinic. See Figure 5.1 for participant flow.

Figure 5.1
Participant Flow



Analyses

Primary outcome variables were AB and craving. To test effects of the AR on AB (speeded detection and difficulty to disengage) and craving factors, we performed analyses of covariance (ANCOVA) with pre-test scores for each variable as covariate to increase statistical power (Van Breukelen, 2006), and group as between-subject factor. Since the DAQ factor 'desire to drink' was highly skewed, results were analyzed with non-parametric Mann-Whitney tests, comparing groups (AR, control) at post-test. These analyses were performed using an intent-to-treat procedure, last observation carried forward for missing data.

To compare participants from the AR and control group on the secondary variables, time to lapse and time to relapse, a Linear-by-Linear Association test was performed. As an indication of a positive AR effect on the standard treatment, we analyzed whether AR participants were sooner discharged after a successful treatment from the clinic than control participants. We performed an exploratory ANCOVA with post-intervention treatment duration (post-ITD) as dependent variable, pre-intervention treatment duration (pre-ITD) as covariate and group as between-participants variable. Since we had a three month follow up, only data from the Heerlen clinic were analyzed (the other clinics had six-month treatment programs). Pearson's correlation coefficient (r) is used as a measure of effect size. Spearman's correlation coefficient (ρ) was used for correlations with pre-intervention treatment duration which was skewed for the complete sample.

Results

Attentional Bias

ANCOVA showed that groups' speeded detection did not differ on old pictures, F (1, 40) = 0.69, p = 0.41, r = 0.13, nor on new pictures, F (1, 23) = 1.76, p = 0.20, r = 0.26. Groups did differ on the difficulty to disengage, both on old stimuli, F (1, 40) = 7.54, p < 0.01, r = 0.39, and on new stimuli, F (1, 23) = 6.52, p = 0.02, r = 0.46 (see Table 5.2 for mean scores). This indicated that the AR was effective in reducing the difficulty to disengage

from alcohol-related stimuli (Figure 5.2), and this effect generalized toward stimuli that had not been used during the training. Available case analyses on old pictures revealed similar patterns of results.

Table 5.

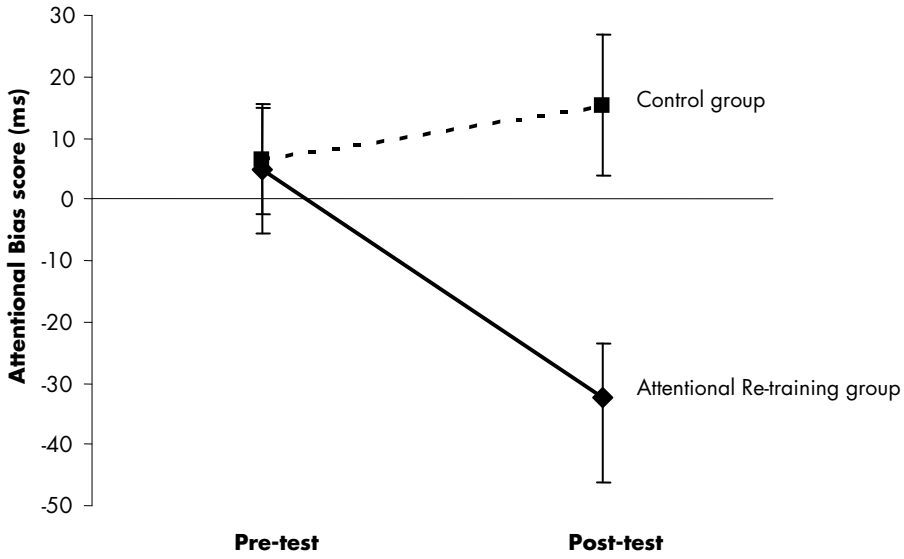
Post-test and Follow-up Mean (SD) Scores per Group

	Attentional Re-training			Control		
Variable	M	SD	N	M	SD	N
Attentional Bias (ms)						
Speeded detection old pictures [a]	-18.06	42.08	21	-3.15	54.68	22
Speeded detection new pictures	-10.19	32.95	12	12.90	47.57	14
Difficulty to disengage old pictures [a]	-32.33	64.19	21	15.30	53.94	22
Difficulty to disengage new pictures	-51.43	79.68	12	27.79	73.44	14
Craving						
Mild and strong desires (scale range 1-7) [a]	1.58	0.99	21	1.56	1.05	22
Reinforcement (scale range 1-7) [a]	2.74	1.99	21	2.73	1.74	22
Subjective control (scale range 1-7) [ab]	5.48	2.02	21	5.06	1.95	22
Follow-up						
Time to lapse (in months)	2.75	0.50	4	1.25	0.50	4
Time to relapse (in months)	2.75	0.50	4	1.50	0.58	4
Post-intervention treatment duration (in days) [a]	42.44	24.28	9	70.75	18.39	8

Note: [a] Missing data imputed as last observation (data from pre-test) carried forward.

[b] A higher score indicates lower perceived control.

Figure 5.2
Attentional Bias Scores for the Difficulty to Disengage, before and after the Intervention.



Craving

On the factor 'desire to drink', 77 % of the sample scored below 2 at pre-test and 81% scored below 2 at the post-test. The Mann-Whitney analysis indicated no group difference on 'desires to drink' at post-test, $Z = -0.13$, $p = 0.99$, $r = 0.02$. ANCOVA's showed that group effects on negative reinforcement, $F\ (1, 40) = 2.92$, $p = 0.10$, $r = 0.26$) and perceived control, $F\ (1, 40) = 3.75$, $p = 0.06$, $r = 0.29$, were non-significant (Table 5.2). Available case analyses revealed similar patterns of results.

Lapse, Relapse

In the group of patients for whom we had lapse and relapse data, four out of 16 AR participants (25 %) and four out of 19 control participants (21 %) had lapsed and relapsed after completing the intervention. In the first month, three control participants had lapsed and two had relapsed. In the second month, one control and one AR participant had lapsed; two controls and one AR participant had relapsed. In the third month, three AR participants had lapsed and relapsed. Exploratory analyses indicated a significant longer time to lapse and relapse in the AR group (respective linear-by-linear association values: 5.25, $p = 0.02$; 4.49, $p = 0.03$) (see Table 5.2 for mean scores).

Post-intervention Treatment Duration

Of the 23 patients in the Heerlen clinic, two (one AR, one control) had dropped-out of the intervention, and four (two AR, two control) had left the clinic against the advice of his/her therapists. Results from the exploratory ANCOVA on the remaining 17 patients (nine AR, eight control) indicated that patients in the AR group were significantly sooner discharged from the clinic after a successful treatment than patients in the control group, F (1, 14) = 6.74, $p = 0.02$, $r = 0.56$ (see Table 5.2 for means).

Additional Analyses

For the complete sample (N = 43), different background variables and craving factors were correlated with speeded detection and difficulty to disengage at pre-test. Perceived control over drinking was positively correlated with the difficulty to disengage, $r = 0.32$, $p = 0.04$, indicating that increased difficulty to disengage corresponds to lower feelings of control. Each type of AB was positively correlated with pre-ITD (speeded detection: $\rho = 0.35$, $p = 0.02$; difficulty to disengage: $\rho = 0.37$, $p = 0.02$), suggesting that AB increased during treatment. All other correlations did not reach significance.

Discussion

The main findings of the AR intervention were a generalized decrease in the difficulty to disengage attention from alcohol-related stimuli, measured three to four days after the

intervention, and an earlier discharge from treatment for the AR group compared to the control group in the patients with the shortest regular treatment program. There was no AR effect on craving. Further, the data suggest that the AR postponed lapse and relapse, although this was explored on a very small subset in our sample.

The generalization of the AR effect toward novel stimuli is clinically important since patients should be able to disengage from all alcohol-related stimuli, not just those trained during the intervention. We believe that the use of many training stimuli required participants to develop a general strategy to disengage from all alcohol-related stimuli. Theoretically, generalization rules out the alternative explanation that the AR effect is a desensitization effect by repeated exposure (Dandeneau et al., 2007). The fact that the AR did not reduce speeded detection of alcohol cues, suggests that participants first scanned the pictures before being able to avoid the alcohol picture. This indicates that a certain amount of control is needed to disengage from alcohol-related stimuli and the reduction in AB is not entirely automatic.

The importance of targeting AB directly is supported by the present study. Earlier it was shown that an increase in AB during treatment increases the chance of relapse (Cox et al., 2002). Our results show a positive relation between AB at pre-test and the treatment duration before pre-test, suggesting that AB indeed increases during regular treatment, and that it is not reduced by counseling (cf. McNally, 1995; Öhman, 1996). Our finding that patients in the AR group (re)lapsed later compared with patients in the control condition, should be considered as a promising preliminary finding. However, the number of participants in the lapse and relapse analyses were too small to control for potentially moderating variables. Furthermore, the percentage of participants relapsing in the AR group was slightly higher than in the control group (25 vs. 21 %).

Within our follow-up period, patients from the clinic with a regular treatment program of approximately three months could be tested on treatment duration after our intervention. On average, patients in the AR group were discharged earlier from treatment than control patients. Discharge was advised by the therapists when he or she considered a patient as being successfully treated. This suggests that the AR has a positive effect on the regular treatment program. Future studies might address the exact mechanism underlying

this effect. We propose that it might be a reduced vulnerability for alcohol cues that influenced patients' treatment progress.

Recent evidence suggests that AR affects the *vulnerability* to respond emotionally instead of affecting conscious emotional states directly (Goetz, Robinson, & Meier, 2008). Future studies might measure craving in situations that potentially trigger craving, for example in a controlled experimental setting, or by using a questionnaire that asks for craving experiences in the last week (Anton, Moak, & Latham, 1996).The lack of a significant direct effect on craving might be because only a very small proportion of our sample reported any desire for alcohol, which is not an uncommon finding in alcoholic patients (cf. Mezinskis, Dyrenforth, Goldsmith, & Somoza, 1998).

In sum, following promising effects of anxiety AR in non-patient samples and small clinically relevant effects in social drinkers, this first patient study provides tentative evidence for the clinical usefulness of an AR intervention in the treatment of substance dependence. The alcohol-AR intervention decreased AB, and data suggest a positive effect on general treatment success. Future studies should focus on the underlying mechanisms of AR and effects on other clinical outcome measures. Additionally, our findings might stimulate research on attention training in patients in treatment for other forms of psychopathology as well.

CHAPTER 6
General Discussion

Summary of findings

The overall goal of the research bundled in this thesis was to increase the scientific knowledge about the changeability of attentional bias for alcohol-related stimuli. Attentional bias in addiction, the excessive selective attention for addiction-related objects, is related to the maintenance and development of addictive behaviours. Two lines of research were conducted for this thesis. The first (see Chapters 2 and 3) was aimed at broadening the knowledge on alcohol prime effects in social drinkers on various aspects of appetitive motivation: attentional bias, eye movements, approach bias and craving. The second line of research (see Chapters 4 and 5) focused on a method to decrease attentional bias and related clinical factors.

In the study described in Chapter 2 (published as Schoenmakers, Wiers, & Field, 2008), we found that the maintenance of attention, the gaze dwell time and number of first eye movements toward alcohol-related stimuli were all increased after a consumption of a low dose of alcohol as compared to a placebo drink. Unexpectedly, there was no larger approach bias after the low alcohol dose. We did, however, measure an increase in craving after the alcohol dose that was not found after the placebo drink. Overall, this suggests an increase in appetitive motivation for alcohol after a low prime dose of alcohol. Additionally, attentional bias and approach bias were correlated much higher after the prime dose than after the placebo.

In a second study on alcohol prime effects (Chapter 3), we measured appetitive motivational constructs following alcohol consumption in a real-life setting. Previously, lab studies had shown changes in craving and attentional bias after prime doses, but no research had been conducted that tested whether these effects could also be measured in a real-life setting, and to what extend these changes relate to alcohol-consumption levels in real-life. We tested an opportunistic sample of social drinkers in a pub. Controlling for usual drinking behaviour, we found increases in craving up to very high alcohol doses. We did not find a significant relation between attentional bias and alcohol consumption in participants who had been drinking less than a binge at the time of testing (less than 6 drinks for males, less than 5 drinks for females). However, for people who had been

bingeing attentional bias was negatively correlated with the amount of alcohol consumed. The results indicate that different aspects of appetitive motivation respond differently to alcohol priming, and they might subsequently affect alcohol consumption in a different way.

The second line of research of this thesis focused on a method to decrease attentional bias. In a computer task, participants are trained to avoid alcohol-related stimuli; it is therefore also called 'avoid-attention modification training' (avoid-AMT)[8]. In a first study in the lab with male heavy drinkers (Chapter 4, published as Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007), attentional bias decreased after the avoid-AMT, but only for the specific stimuli used in the training. There were no effects on untrained stimuli and no effects on a second measure of attentional bias. Also, craving and drink preference were not affected by the training. Thus our first avoid-AMT did not reveal clinically relevant effects, and no evidence for a causal relation between attentional bias and craving. The latter would have been the case when the training (i.e. manipulation) of attentional bias had resulted in a contingent effect on craving.

Although our own results (Chapter 4) were not very promising at first glance, more AMT studies – to decrease and increase attentional bias - had been conducted in the meantime that did show effects on subsequent measures of disorder-related symptoms (e.g. Dandeneau & Baldwin, 2004; Field & Eastwood, 2005; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Wiers, Cox et al., 2006). We reasoned that by increasing the intensity of the avoid-AMT (by increasing the number of training stimuli and sessions, and by motivating participants to perform better), a stronger effect could be obtained. In the second avoid-AMT study (Chapter 5), we trained alcoholic patients from three addiction treatment centres in five re-training sessions. This intervention was successful in decreasing attentional bias for trained and untrained stimuli, indicating that attention for the complete category of alcohol-related stimuli had been changed. Patients reported hardly any craving at pre-test which might explain why we did not find decreased craving after the

[8] Many different terms have been used for this kind of training; in Chapters 4 and 5, it is referred to as 'attentional re-training'. Again other researchers have called it 'attentional bias reduction training' (Dandeneau, 2004).

intervention. In the clinic with the shortest regular treatment program, patients in the avoid-AMT group were much sooner discharged than patients in the control group, suggesting that the training had a positive effect on the regular treatment program that was mainly focused on cognitive behavioural therapy. Finally, of the few patients who relapsed after the treatment program, patients in the re-training group relapsed at a later time than patients in the control group, indicating that the training had a positive effect on time to relapse.

In this general discussion, I will first discuss alcohol prime studies. Then, I will review attention training studies including the ones in this thesis. The review is focused mainly on clinically relevant attention training methods.

Alcohol prime studies

Different prime effects on attentional bias and craving

The first to study effects of alcohol priming on attentional bias in a sample of social drinkers were Jones and Schulze (2000). They measured attentional bias by means of an addiction-Stroop task, and found more interference for positive alcohol-related words in participants who had consumed an alcoholic drink compared to participants who had consumed a soft drink. This indicated preferential processing of positive alcohol-related stimuli after a low alcohol dose. Duka and Townshend (2004) studied effects of alcohol priming on attentional bias using a visual-probe task with 500 ms stimulus presentation duration. In this study, attentional bias was higher in participants who had consumed a low alcohol dose than in those who had consumed a placebo drink or a moderate dose. They inferred from these findings that attentional bias follows an inverted U-shape curve during alcohol consumption, increasing first and then decreasing. In our lab study (Chapter 2) we also found greater attentional bias after a low prime dose than after a placebo drink in heavy social drinkers. We measured attentional bias with a visual-probe task (stimulus presentation duration: 2000 ms) and measured concurrent eye movements. Data showed

longer gaze dwell time and more first eye movements towards alcohol-related stimuli following the low prime dose compared to the placebo drink.
In a subsequent field study (Chapter 3), we measured attentional bias with a flicker paradigm (cf. B. T. Jones, Jones, Smith, & Copley, 2003). In our version of this task, participants had to detect a changing object (alcohol-related in one trial, neutral in another trial) in a picture composed of alcohol-related and neutral objects. A faster detection of the alcohol change than of the neutral change indicates an attentional bias. The data did not show a significant increase in attentional bias after low doses of alcohol (possibly because of relatively few participants in the low-dose group), but did show a significant decrease after higher doses. Taken together, most evidence indicates that attentional bias follows an inverted U-shaped curve in response to increased alcohol intake. At the same time, subjective craving seems to increase from low up to very high doses (see Chapter 3 for an overview of prime effects on craving). In the discussion in Chapter 3 we offered two possible explanations for this difference.

Firstly, subjective, conscious feelings of craving (measured by questionnaires) may be affected by different factors than relatively automatic reactions, such as attentional bias. In addition, research has shown that stimulant and sedative effects can occur simultaneously after increased ingestion of alcohol (Earleywine & Erblich, 1996). It is possible that attentional bias is affected by a basic affective reaction to which sedation contributes increasingly more after more alcohol, leading to a decrease in the incentive value of alcohol cues. Craving, in contrast, might be affected by more conscious, elaborative cognitive processes and interpretations of one's own state. These interpretations can be biased by situational factors. A positive drinking environment and positively framed craving questionnaires ('How much do you crave alcohol?' instead of 'How much do you *not* crave alcohol?') could focus participants on the positive and more arousing feelings and cognitions. As a result, positive arousing effects become more prominent than negative sedative effects, resulting in increased desire or craving for alcohol. To test this idea, future studies should include measures of the motivation *not* to drink (e.g. McEvoy, Stritzke, French, Lang, & Ketterman, 2004) and measures of subjective intoxication effects (e.g. Duka, Stephens, Russell, & Tasker, 1998; Earleywine & Erblich, 1996).

A second possible explanation concerns the difference between responses to alcohol cues on the one hand, and the internal stimulus properties of alcohol and the act of drinking on the other hand. An increased salience of drug related cues (as reflected by AB) is functional in drug seeking (Robinson & Berridge, 2000), since it increases the chance of detecting the drug. When one desires an unavailable drug, drug related cues may become sensitized (Morgan, Smith, & Roberts, 2005) and attract more attention (Field, Mogg, Zetteler, & Bradley, 2004; Gross, Jarvik, & Rosenblatt, 1993; Mogg & Bradley, 2002), which in turn facilitates alcohol seeking. After some drinks, subjective intoxication effects increase and it becomes evident that alcohol is easily available. Then, the saliency of alcohol cues loses its function and attentional bias decreases. This could be tested experimentally by manipulating the perceived availability of alcohol during various stages of intoxication. With low perceived availability, attentional bias should increase up to higher levels than with high perceived availability.

At the same time, while attentional bias decreases after a moderate alcohol dose, the incentive value of alcohol (i.e. ethanol) and the reinforcing effects of drinking may still increase. Alcohol has positive direct effects on one's subjective state: indirect evidence comes from research on alcohol expectancies showing that drinking is mainly predicted by positive outcome expectancies, and less by negative expectancies. If these expectancies are based on people's past experiences with drinking, these positive alcohol-related effects might actually occur during a drink occasion. Additionally, alcohol consumption has been found to decrease negative mood in the presence of alcohol cues (Davidson, Tiffany, Johnston, Flury, & Li, 2003). Further, Gilman, Ramchandani, Davis, Bjork, and Hommer (2008) found that intravenous administration of alcohol activates striatal reward circuits in the brain. They suggested that this activation contributes to subjective pleasure since it was related to self-rated intoxication. Altogether, these positive alcohol-related effects might reinforce the consumption of alcohol. Thus, as long as people experience the effects of alcohol as positive, and these effects become stronger with increased consumption, increased consumption leads to increased desire for alcohol. In addition, alcohol affects reward circuitries in the brain more than non-alcoholic drinks, possibly explaining why satiation does not occur after a few alcoholic drinks. A recent neuroimaging study in heavy drinkers demonstrated that the neural system related to incentive salience, i.e. the

mesocorticolimbic circuitry, showed a stronger activation after tasting alcohol than soft drinks and this activation was positively related to self-reported urge (Filbey et al., 2008). In sum, while alcohol *cues* become less determining in increased alcohol use during one occasion, *consuming* alcohol still determines the motivation or urge to drink.

Real-life setting

Many laboratory studies on prime effects on the desire (i.e. craving) for alcohol and some on attentional bias have been reported (for reviews, see de Wit, 1996; Field, Schoenmakers, & Wiers, 2008). These studies stem from the tradition to study alcohol prime effects in order to understand why abstinent alcoholics relapse after just one alcoholic drink. However, although these studies are important in understanding prime effects, I believe that especially in the case of social drinkers, a laboratory setting misses many aspects that are present in real life which influence why people keep on drinking after one drink. For an alcoholic, the drink alone might be a sufficient stimulant to keep on drinking; for a social drinker, the drink probably has considerable influence, but the drinking behaviour of others might just as well cause him to drink (Bot, Engels, Knibbe, & Meeus, 2007). Further, we know that alcohol-related cues prime appetitive motivation to drink (e.g. Cox, Yeates, & Regan, 1999), and these cues are relatively absent in a laboratory, but omnipresent in a pub.

In our field study, we did not detect increased attentional bias after low doses of alcohol. Perhaps the sub-sample that had been drinking only a few drinks was too small to detect such an effect. Additionally, we did not measure relevant factors such as the number of people participants were drinking with, nor did we measure whether the breath alcohol level of participants was falling or rising, which has differential effects on stimulant or sedative sensations (Earleywine & Erblich, 1996; Holdstock & de Wit, 1998). Future studies should include more participants and measure other aspects that contribute to consumption levels as well. Furthermore, in the correlational design we used, we cannot make causal inferences about whether attentional bias or craving increased drinking, vice versa, or both. Attentional bias may be a causal agent during a drinking episode, but might also be a mere effect of drinking or index for the underlying appetitive motivational

process. I believe it is important to investigate the causal role of attentional bias during drinking episodes, for example by testing whether alcohol consumption could be predicted from a change in attentional bias over time. It would also be interesting to know whether and how the decrease in attentional bias after a relatively high alcohol dose influences drinking behaviour.

Appetitive motivation revisited

In this thesis I used the umbrella term 'appetitive motivation', or 'appetitive motivational system' for attentional bias, approach bias and subjective craving. These three processes, however, are not always found to be correlated (for an overview see introduction of Chapter 2) and do not always change concurrently after an experimental manipulation (see review on attention modification training later in this chapter). In the study described in Chapter 3, craving and attentional bias did not correlate, and attentional bias and approach bias were only correlated after a prime dose, but not after a placebo drink.

Partly, these mixed findings regarding correlations or concurrent changes in the three processes might be due to the fact that these processes themselves are not unitary constructs. Craving has been defined in many different ways and consequently measured with many different questionnaires. For example, craving has been measured with single item visual analogue scales ('Please rate your urge to drink right now'), and with multi-item questionnaires measuring different craving factors. One such questionnaire is the Desires for Alcohol Questionnaire (DAQ; Love, James, & Willner, 1998) that measures mild desires, strong desires, perceived control over drinking and reinforcement. Another multi-factorial questionnaire is the Alcohol Craving Questionnaire (ACQ; Singleton & Gorelick, 1998; Singleton, Henningfield, & Tiffany, 1994) that distinguishes between emotionality, purposefulness, compulsivity and expectancy. Additionally, the Approach and Avoidance of Alcohol Questionnaire (AAAQ; McEvoy et al., 2004) measures the subjective motivation to drink and to *not* drink.

The same holds for attentional bias. Whereas with an addiction-Stroop paradigm cognitive interference for substance-related stimuli is measured, with a visual-probe paradigm and flicker paradigm the spatial allocation of attention toward substance-related

stimuli is measured. Spatial attentional bias is further specified by looking at the time course of attention. The time course is a continuous process in which certain stages are distinguished, such as the early detection of cues, attentional maintenance, and the difficulty to disengage. Approach bias has also been measured with different tasks: the Stimulus Response Compatibility task (De Houwer, Crombez, Baeyens, & Hermans, 2001; Mogg, Bradley, Field, & De Houwer, 2003), and the Approach Avoidance Task (AAT; Rinck & Becker, 2007; see also Wiers et al., 2008).

All these different questionnaires and tasks possibly measure different aspects of appetitive motivational processes. Further, there may be individual differences in types of attentional bias, approach bias and craving (Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005; Potgieter, Deckers, & Geerlings, 1999; Verheul, van den Brink, & Geerlings, 1999) that obscure the relation between these constructs in correlational studies. Additionally, different situations or cues might have different effects on the different processes. According to the Incentive Sensitization theory (Robinson & Berridge, 2000), cues might trigger approach responses and guide behaviour without evoking conscious craving.

On a methodological level, different findings with similar tasks might be caused by the amount of control one has over performing a reaction time task. For example, to explain the increase in correlation between attentional bias and approach bias in Chapter 2, we suggested that reaction time tasks best measure the underlying construct when there is no attempt to control responses during the task. Alcohol decreases inhibitory control (Fillmore & Vogel Sprott, 1999, 2000, 2006; Fillmore, Vogel Sprott, & Gavrilescu, 1999) and will therefore influence the performance on the reaction time tasks that now better reflect the underlying construct, appetitive motivation (Chapter 3).

Taken together, the term ‘appetitive motivation’ should not be regarded as a unitary construct. Rather, it consists of different processes that either have a concurrent or independent effect on substance use and drug-seeking behaviour. As such, appetitive motivation can be defined as any process that is causally related to the motivation to pursue addictive substances.

Review attention Modification studies

Since MacLeod and colleagues (2002) published their seminal research paper on the attention modification training (AMT; see also Harris & Menzies, 1998), there has been a steady growth in the number of studies on this paradigm. In this part of the general discussion, I will review the AMT studies in addiction that have been published or accepted for publication since, including the studies reported in Chapters 4 and 5 of this thesis and one in which I was involved, which is currently under review (Field, Duka, Tyler, & Schoenmakers). The review starts with a short introduction in AMT and description of different types of AMT. Then, the AMT studies and results are described. A subsequent part is devoted to methodological issues in AMT research, dealing with design, dependent variables to account for generalization of AMT effects, contingency awareness, and clinical relevant effects. Finally, a model is proposed that explains how a clinical relevant AMT could lead to decreased vulnerability for addictive behaviour.

Introduction in Attention Modification Training

Attentional bias can be defined as excessive selective attentional processing of disorder-related cues. It has been linked to the development and maintenance of a number of mental disorders, such as anxiety disorders (for a review see Bar-Haim, Lamy, Pergamin, Bakermans Kranenburg, & van Ijzendoorn, 2007), depression (for a review see Mogg & Bradley, 2005), eating disorders (e.g. Smeets, Roefs, Van Furth, & Jansen, 2008), and addiction (see Field & Cox, 2008, for a review). Although attentional bias is related to these disorders, it could be that it is merely an unimportant side-effect or an indication of the severity of the disorder, but not a causal factor (Hogarth & Duka, 2006).

An experimental manipulation of attentional bias and assessment of consequent changes in disorder-relevant symptoms is the best test of causality. In 2002, MacLeod and colleagues published the first research paper on attention modification training (AMT). An AMT temporarily affects attentional bias for disorder related stimuli. MacLeod et al. increased attentional bias for threatening stimuli in one group and decreased it in another group. After the attention training, they found congruent increases and decreases in emotional vulnerability. This way, they demonstrated that attentional bias was causally

related to anxiety. Later, a causal role for attentional bias was demonstrated by using AMT in alcohol abuse (Field, Duka et al., 2007; Field & Eastwood, 2005), and body dissatisfaction (Smith, Dip Sci, & Rieger, 2006). Another study found that the AMT could be used as an index for the susceptibility to trait anxiety; participants whose attentional bias was easily manipulated were also more likely to develop trait anxiety in response to stress (Clarke, MacLeod, & Shirazee, 2008).

Next to using AMT to test the causal role of attentional bias, it also offers possibilities to be used as a clinical tool, namely to decrease attentional bias. Mathews and MacLeod (2002) described some preliminary studies with clinical effects on anxiety. After repeated training sessions, they measured decreases in attentional bias and trait anxiety in participants who had elevated trait anxiety scores before testing. We (Chapter 4) did not find clinically relevant effects of AMT for alcohol in heavy social drinkers. However, in alcoholic patients, preliminary clinical effects were found (Chapter 5). Using a different paradigm, Fadardi and Cox (2007; see also Wiers, Cox et al., 2006) also reported clinical relevant effects after repeated training sessions.

Taken together, while AMT started as an experimental manipulation to temporarily change attentional bias, it now seems to develop into a clinical treatment tool. Findings of attentional bias in addicted patients (B. T. Jones, Bruce, Livingstone, & Reed, 2006; Stetter, Ackermann, Bizer, Straube, & Mann, 1995), of increased attentional bias during treatment (Chapter 5; Noël et al., 2006), of relations between poor treatment success and attentional bias (Carpenter, Schreiber, Church, & McDowell, 2006), and of relations between relapse and attentional bias (Cox, Hogan, Kristian, & Race, 2002; Marissen et al., 2006; Waters et al., 2003), all suggest that a tool to directly target and decrease attentional bias is a valuable addition to the treatment of addiction.

Different Types of Attention Modification Training

AMTs are typically based on attentional bias measures, with the visual-probe classification task most frequently used (Bradley, Mogg, Falla, & Hamilton, 1998). In the visual-probe classification task, two stimuli representing two categories (disorder-related and neutral) are presented simultaneously on a computer monitor. After a short interval the stimuli

disappear, and a probe (e.g. an arrow pointing up or down) replaces one of the stimuli. Participants have to classify the probe (as pointing up or down) as quickly as possible by pushing one of two buttons. Faster responses to probes replacing disorder-related stimuli is an indication of attentional bias.

During all trials of a visual-probe task, probes will replace disorder-related with equal frequency as neutral stimuli. In a visual-probe AMT, probes mostly replace stimuli of only one category. It is hypothesized that attentional bias is increased during an 'attend'-AMT, in which probes replace disorder-related stimuli in most of the trials. In an 'avoid'-AMT (i.e. attentional *re*-training), probes replace neutral stimuli in most of the trials, thereby decreasing attentional bias.

Another type of AMT that affects the spatial movement of attention was developed by Dandeneau and colleagues (Dandeneau & Baldwin, 2004; Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007). This AMT has not been used in addiction research. In this 'matrix'-AMT, participants repeatedly had to detect an acceptance-expressing face in a 4x4 matrix of frowning faces. During the training, participants had learned to inhibit socially rejecting information, reflected by decreased attentional bias scores on an emotional Stroop task. Thus far, this matrix-AMT has not been studied in addiction research.

Fadardi and Cox (2007) developed an alcohol-AMT based on the alcohol-Stroop task (Johnsen, Laberg, Cox, Vaksdal, & Hugdahl, 1994; Stetter et al., 1995), a presumed measure of attentional bias for alcohol. In the computerized version of the Stroop task, alcohol-related and neutral words are presented one by one in different colours on a computer screen (for a picture-version of this task, see Bruce & Jones, 2004). Participants are instructed to name the colour of the word as quickly as possible, and to ignore the semantic meaning of the word. Someone who has an attentional bias for alcohol-related stimuli will be slower in colour-naming alcohol-related stimuli than neutral stimuli. This interference by alcohol-related stimuli leads to the Stroop-effect, i.e. the difference in response latency between alcohol-related and neutral stimuli. In the Stroop-AMT, named the 'Alcohol Attentional Control Training Program' (AACTP), participants with an attentional bias are trained in colour-naming by repeated practice of the task and motivational feedback on their performance. Participants have to name the colour of the background or frame

around alcohol-related photographs. Attentional bias is expected to be reduced by this training.

Differences in attentional bias

This review focuses on AMT in research on addiction. Since AMT did not origin in addiction research but in anxiety research (MacLeod et al., 2002), I have already discussed AMT in other domains of psychopathology. The nature of attentional bias, however, differs between anxiety and addiction. First of all, the disorder-related stimuli are different; in anxiety, attentional bias has been found for aversive, threatening stimuli (e.g. MacLeod, Mathews, & Tata, 1986). In contrast, in addiction, attentional bias has been found for appetitive stimuli (e.g. Townshend & Duka, 2001). Additionally, stimuli in anxiety AMTs are words, while in addiction-AMTs pictures are used. Pictures are more ecologically valid, but also more specific; a picture of a beer can, for example, is relevant to someone who is used to drinking from such a beer can but not to someone who drinks beer from another brand. Words are less specific, can therefore be interpreted in multiple ways and consequently relate easier to more persons; the word 'fear' (anxiety-related) can refer to many different situations for different people. Possibly, it is more important for pictures than for words in an attentional bias task to be individualized (Fadardi, Cox, & Klinger, 2006).

Further, the time course of attention possibly differs between disordered people in these domains. By using different stimulus presentation durations in a visual-probe task, one measures different aspects of attention, since the spatial focus of attention is measured at the moment of stimulus offset, when the probe appears. Knowledge of attentional focus on different stimulus presentation durations gives an indication of the time course of attention. When stimuli are presented very shortly (e.g. 50-200 ms) the speeded detection of disorder-related stimuli is measured. With a relatively long stimulus presentation duration (e.g. 1,000-2,000 ms), the maintenance of attention is measured, and with a medium long duration (e.g. 500 ms) a delay in disengagement or difficulty to disengage attention from disorder-related stimuli is measured. In addiction, heavy social alcohol-drinkers often show attentional bias at 500 ms and longer (Field, Mogg, Zetteler et al.,

2004; Townshend & Duka, 2001). Little research has been conducted on the visual-probe task with alcohol dependents in treatment. Noël et al. (2006) found speeded detection in a sample of alcoholic patients (50 ms), but no overall difficulty to disengage (500 ms) or maintenance (2,000 ms). Townshend and Duka (2007) found avoidance from alcohol-related stimuli at a stimulus presentation duration of 500 ms in a sample of alcoholic patients. Avoidance is indicated by slower reaction times in congruent trials (in which the probe replaces the alcohol-related stimulus) than incongruent trials (in which the probe replaces the neutral stimulus). Smokers have been found to show attentional bias (i.e. approach) at longer stimulus durations (500 ms and 2,000 ms; Bradley, Mogg, Wright, & Field, 2003).

The lack of a bias in later stages of attentional processing (>500 ms) in addictive patient samples has been suggested to result from conscious efforts to avoid disorder-related stimuli in order to not be affected by those stimuli and to prevent relapse (Stormark, Field, Hugdahl, & Horowitz, 1997). Stroop studies in addicted patients suggest, however, that addictive patients do have difficulties ignoring addiction-related stimuli that are in the centre of their visual field (Bauer & Cox, 1998; Franken, Kroon, Wiers, & Jansen, 2000; Lubman, Peters, Mogg, Bradley, & Deakin, 2000; Vadhan et al., 2007). Even though it has not been measured yet, it may be that addicts who are not in treatment do show a slow bias as measured with a visual-probe. These people are not necessarily motivated to remain abstinent, and may have difficulties avoiding addiction-related stimuli.

In patients with anxiety disorders, biases in earlier stages of attentional processing (short stimulus presentation durations) have been found, even with subliminal stimulus presentation (for a review see Bar-Haim et al., 2007). At longer stimulus presentation durations, patients with an anxiety disorder find it hard to disengage from disorder-related stimuli, i.e. negative stimuli for generalized anxiety disorder. The time course for addictive people (not in treatment or no motivation to abstain) and highly anxious people might be alike: an early engagement toward disorder-related stimuli, and a delayed disengagement or difficulty to disengage from those stimuli (also see Fox, Russo, Bowles, & Dutton, 2001).

These differences between addicts, heavy social substance-users, and patients with an anxiety disorder should be kept in mind when interpreting AMT results for different kinds of disorders and different types of substance users. It might be appropriate to adjust the

stimulus presentation duration of the AMT to a stimulus duration that is equal to or shorter than one with which a detrimental bias has been found. However, as I will discuss later in this review, AMT might not necessarily work by directly changing attentional bias, but rather by increasing control over attention. In that case, differences between disorders and stimulus presentation durations should be less relevant.

Overview of Addiction-AMT studies

A schematic overview of addiction-AMT studies is presented in Table 6.1. In the first published addiction-AMT study (Field & Eastwood, 2005), a group of heavy social drinkers was trained either toward or away from alcohol-related stimuli. After the AMT, attentional bias in the 'attend' group had increased while it had decreased in the 'avoid' group. Further, craving in the attend group was higher than in the avoid group after the training and the attend group drank significantly more alcohol in a bogus taste test than the avoid group. This study hereby demonstrated a causal effect of attentional bias on addiction related variables, craving and drinking behaviour.

The second published study was concurrently performed in our own lab (Chapter 4). We trained one group away from alcohol-related stimuli and toward soft-drink stimuli. A control group performed a prolonged visual-probe task, i.e. with a 50/50 division of probes over alcohol and soft-drink stimuli, over all trials. We found a decrease in attentional bias for the stimuli that were used in the training. In addition, we measured effects on attentional bias for new (i.e. untrained) stimuli as well, but there were no effects on those stimuli. Further, we did not find effects on craving, or preference for a soft drink over alcohol. After excluding participants who were aware that their focus of attention was measured in the visual-probe task (13%), results did not change. None of the participants reported awareness of the experimental contingencies in the AMT.

Field and colleagues (Field, Duka et al., 2007) subsequently published a paper on an AMT study with three experimental conditions: an 'attend' (alcohol) group, an 'avoid' group (i.e. attend neutral), and a 50/50 control group. In this study, they used untrained stimuli as well, both in the pre-test and the post-test visual-probe. This allowed them to measure changes in attentional bias for untrained stimuli instead of merely comparing

untrained stimuli between groups after the AMT. They did not replicate their earlier findings on craving and drinking behaviour (Field & Eastwood, 2005). Craving did increase for participants in the 'attend' group who had been aware of the experimental contingencies (78%). Further, hypothesized effects on attentional bias for new pictures were found only in the attend group.

Field et al. (under review) performed a visual-probe AMT in smokers. The design was similar to the study by Field, Duka et al. (2007). In addition, stimulus presentation durations were 50 and 500 ms, however, there were no significant interactions for duration thus data were collapsed across 50 and 500 ms. Results indicated increased attentional bias from pre- to post-test in the 'attend' group for old (i.e. trained) stimuli, but no changes in the 'avoid' and control group. There were no effects for new stimuli in any of the groups. Furthermore, no training effects on craving were found, only a general increase in craving from pre- to post-test. As for the behavioural measures, there were no group differences in the amount participants were willing to pay for a cigarette, and no group differences in the number of cigarettes that participants smoked within 30 minutes after the training session. Finally, there was a statistical trend in group difference for the hypothetical choice over smaller amounts of cigarettes immediately and larger amounts after a delay (delay discounting); compared to the other groups, the attend group showed higher delay discounting, suggesting a higher motivation to smoke.

Results from these four studies suggest that is easier to increase than to decrease attentional bias. This could be due to a priming effect, which is stronger in the 'attend' groups than the other groups. Alternatively, it could be caused by a very low or absent attentional bias and craving in these participants before the AMT, which could therefore not be further reduced. Lastly, reinforcing an existing response, i.e. focusing on substance-related stimuli, may be easier than weakening this response.

In the former studies, participants were left blind for experimental contingencies. In the two studies discussed hereafter, participants were informed about attentional bias and they were motivated in improving performance on the AMT to decrease their attentional bias. In addition, these studies were partly performed with alcohol abusers and dependents. In preliminary research reports of an AMT study, Fadardi and Cox (2007) reported clinically relevant effects of their Stroop-AMT (described above). Participants in this study

performed four AMT sessions and were given motivational feedback on their progress. After the AMT, they found a decrease in attentional bias for heavy drinkers, abusers and detoxified alcoholics. In the abusers they also measured weekly alcohol consumption following the AMT, and found a decrease in consumption, an increase in their readiness to change and confidence in their ability to control their drinking. These studies, however, lacked control groups, and therefore their effects should be interpreted with caution. Also, merely participating in a program designed to reduce drinking could have been a sufficient incentive to cut-down.

Recently, we performed a clinical study on the visual-probe AMT in alcoholic patients in three clinics in the Netherlands (Chapter 5). This AMT differed from earlier visual-probe AMT studies in a number of aspects. First, the AMT intervention consisted of five training sessions. Secondly, participants were informed that they should try to avoid the alcohol-related stimuli. Third, positive motivational feedback was given on reaction times and goals for faster reaction times were set for the next session. Fourth, many more stimuli were used in the training than in the former study. In addition, the control group performed a computer task that would not affect attentional bias, but did allow us to give similar motivational feedback. After the intervention, we found a strong decrease in attentional bias for old and new pictures in the avoid-training group. Craving was very low at baseline and did not further decrease. There were also some preliminary clinical effects: time to lapse/relapse was longer in the avoid-training group. In the clinic with the shortest regular treatment program, patients in the training group were earlier discharged from treatment than control patients.

In sum, the single-session AMT studies have partly resulted in evidence for the causal relationship between attentional bias, craving and substance use. However, the effects of single-session 'avoid' trainings are rather weak and have not provided much support for the use of AMT as a clinical tool. More extensive AMT interventions aimed at decreasing attentional bias and symptoms related to addiction seem to be more appropriate as a clinical tool, although the evidence is still rather scarce. In the next paragraph, methodological issues are discussed that are important to take into consideration while designing AMT studies.

Table 6.1

Overview addiction-AMT studies

Reference	Substance	Training (stimulus presentation duration)	Participants	Effect on trained stimuli	Effect on Untrained stimuli	Alternative reaction time measure	Clinical outcome measure
Field & Eastwood, 2005	Alcohol	Visual-Probe (500 ms)	Heavy social drinkers (N=40)	Attend group: increased AB Avoid group: decreased AB	-	-	Attend group: increased urge Avoid group: no effect on urge Taste test: attend group consumed more than avoid group
Schoenmakers et al. 2007 (Chapter 4)	Alcohol	Visual-Probe (500 ms)	Heavy social drinkers (N=106)	Avoid group: decreased AB Control group: no effect	(Only post-test) No group difference at post-test	No group difference on post-training flicker paradigm, but an overall AB	No effects on craving or preference
Field et al. 2007	Alcohol	Visual-Probe (500 ms)	Heavy social drinkers (N=20)	Attend group: increased AB Control group: no effect Avoid group: borderline sign decreased AB	Attend group- increased AB Control group - no effect Avoid group - increased AB	No effects Stroop, flicker paradigm, stimulus response compatibility task (approach bias)	Attend group: increased craving for aware participants. (no other craving effects) No effects on taste test.

Fadardi & Cox (2007; in Wiers et al. 2006) study 1	Alcohol	Stroop	Detoxified alcohol abusers (N= not specified)	Overall decrease in interference for alcohol-related stimuli	-	-	Decrease in weekly consumption Increased sense of control over AB and drinking
Fadardi & Cox (2007; in Wiers et al. 2006) study 2	Alcohol	Stroop	Heavy social drinkers (N=54)	(no control group) Overall decrease in interference for alcohol-related stimuli	-	-	Decrease weekly consumption Increased sense of control over AB and drinking.
Schoenmakers et al., under review (Chapter 5)	Alcohol	Visual-Probe (200&500 ms)	Alcoholic patients (N=37)	Avoid group: decreased AB Control group: no effect	(Only post-test) Avoid group smaller bias (negative AB/avoidance) than control group.	-	No craving at pre-test, no training effect. Time to lapse/relapse longer in training group. Shortest regular treatment duration patients: earlier discharge training group.
Field et al. (under review)	Nicotine	Visual-Probe (50&500 ms)	Tobacco smokers (N=72)	Attend group: increased AB Control group: no effect Avoid group: no effect	No effects.	No group effect on alcohol Stroop task.	Main effect: increase in craving from pre-AMT to post-AMT. No group effects

Note: AB = attentional bias

Methodological issues

The AMT studies differ on a number of aspects in their methodology. I will discuss some possible methods to improve AMT study designs which will lead to a better understanding of AMT effects. These issues concern the experimental design and the measurement of additional dependent variables to provide information on generalization of effects, the role of contingency awareness, and clinically relevant effects.

Task specific learning

All AMT studies used the attentional bias task which the training was based upon as dependent measure. For example, most trainings are modified visual-probe tasks, and training effects are often measured with the standard visual-probe task. An alternative explanation for effects found on the attentional bias measure is that mere task-specific learning caused the effect; in other words, during the visual-probe post-AMT test, participants might remember that, during the training, for certain stimulus-pairs the probe had always replaced one of the two stimuli. In the post-test, this may have resulted in participants trying to inhibit focusing on those stimuli that were not replaced by a probe previously during the training. Thus, to perform well, that is to respond as fast as possible to the probe, they will deliberately use task-specific learning strategies during the attentional bias post-training test.

The ultimate test to demonstrate whether attentional bias really changed, is to add untrained stimuli to the pre-AMT test and post-AMT test and to measure attentional bias for those stimuli (Chapter 4; Field et al., under review). In that case, attentional bias is measured for stimuli that participants have not previously been exposed to. In addition, one could also use a different measure of attentional bias (Chapter 4; Field, Duka et al., 2007; Field et al., under review) to control for task-specific learning, since task-specific learning strategies from one task cannot be used for a different task. No effects of AMT, however, have been found on different reaction time measures of appetitive motivation. After a training to decrease alcohol-related approach action tendencies (i.e. approach bias),

Wiers and colleagues did find generalization to another task that measured implicit approach/avoidance associations (Wiers et al., 2008).

In single-session AMT studies, avoid-AMT effects have not been found on untrained stimuli (Chapter 4; Field et al., under review), and there have even been reports of increases in attentional bias for untrained stimuli. This suggests that avoid-AMT effects on attentional bias could have been effects of task-specific learning. We did find effects on untrained stimuli after multiple avoid-AMT sessions, indicating real effects on attentional bias (Chapter 5). In single session attend-AMT groups, effects for new stimuli have not been consistent, in an alcohol AMT effects were found (Field, Duka et al., 2007), but not in a smoke AMT (Field et al., under review).

Time-dependent changes

During performance of an AMT, real changes in attentional bias or craving may occur that are not an effect of attention training. These are either time-dependent changes, such as increases in craving or increases in attentional bias that are caused by abstinence. Or these are prime-effects caused by exposure to substance-related stimuli in the training. I will discuss these effects and solutions to control for these effects successively.

By including an experimental group whose attentional bias is not trained, one controls for time-dependent effects. There two no-training control conditions so far mentioned in AMT studies. One is a 50/50 control group in a visual-probe AMT, where the difference in the training is that the probes are equally divided over the alcohol and neutral category (Chapter 4; Field, Duka et al., 2007; Field et al., under review). In our multiple-session avoid-AMT (Chapter 5), we used a classification task that exposed participants to the same pictures while not influencing attentional bias.

In two studies with no-training 50/50 control groups, time-dependent increases in craving were indeed found, irrespective of experimental group. This was demonstrated by an increase in craving in all groups including the control group (Field, Duka et al., 2007; Field et al., under review). Some early AMT studies did, however, not include a no-training control group. Either effects of avoid-AMT with attend-AMT were compared (Field & Eastwood, 2005), or no control group was included at all (Fadardi & Cox, 2007). Studies

with an avoid/attend design might misinterpret effects on their dependent variables, even if base-line scores of their dependent variables were measured. If, for example, there is an increase in craving scores from pre- to post-test in the attend group, but no increase in the avoid group, this might be interpreted as a greater effect of the 'attend' compared to the 'avoid' training. However, it may very well be that the increase was merely time-dependent (independent of the AMT), and the avoid-AMT prevented an increase in craving in the avoid group. A no-training control group would control for this time-effect.

Prime-by-exposure-effects

There is one problem however, that remains with the control tasks as described earlier, namely prime-by-exposure effects. That is, the amount of priming differs in the different experimental conditions, which may account for some of the effects. The original reason for including a 50/50 control task was that the only difference with the experimental task would be the contingency of the task. Accordingly, participants would be equally exposed to addiction-related stimuli. This line of reasoning might be false though; participants in an attend condition are trained toward addiction-related pictures and are probably longer exposed to those pictures compared to participants who are trained to avoid them or participants in a 50/50 control group. A prime-by-exposure effect explanation can therefore only be contradicted by a sustained change in attentional bias when possible prime effects have disappeared. One could test this by measuring attentional bias a day after the training, or by including a manipulation that neutralizes prime effects but does not affect attentional bias, after the AMT.

We measured AMT effects on attentional bias three to four days after the last training session (Chapter 5). It seems unlikely that those effects could be attributed to a prime-by-exposure effect. Field et al. (under review) found no group effects on attentional bias measures or craving in the second post-test, one day after the training. Thus, their effects might be influenced by priming. Note, however, that this could just as well indicate that the AMT effect did not last one day. Instead of using a control group, Fadardi and Cox (2007) used a baseline attentional bias measure one month before pre-test and AMT. Although

such a design does allow for a comparison between no-training and training, it does not control for prime-by-exposure effects or placebo effects.

Effects on secondary variables such as craving and behaviour could also be explained by mere prime-effects, time-dependent effects, or placebo effects, if not properly controlled. A strong indication of whether craving and behaviour are altered by a change in attentional bias would be a correlation between these variables with attentional bias at post-test. Another indication would be a correlation between the change in craving and the change in attentional bias from pre- to post-test. It has to be noted however, that the absence of such correlations does not imply that the effects are *not* caused by a change in attentional bias, since the effect of attentional bias on craving might differ between participants.

Contingency awareness

Questionnaires and behavioural measures are particularly sensitive to demand effects. For example, when participants realize that they are trained toward substance-related cues, they might think that researchers are trying to increase craving and drinking behaviour. Consequently, the craving questionnaire could be filled out accordingly and participants may use more of the substance in a behavioural measure. Or they might counteract against the supposed hypothesis. More implicit measures, such as attentional bias tasks, are probably less easily controlled by participants and it is less obvious to participants what these tasks are measuring than is the case with questionnaires. Notwithstanding these benefits, one should still be aware of possible demand effects (Steffens, 2004).

Only at the end of the experiment, or after the AMT, researchers can check for awareness of the experimental contingencies. That is, whether participants noticed that the probes during the training were unequally divided over the categories, and if so, whether they had a correct assumption about the goal of the study. However, awareness of the division of probes could even be a prerequisite for AMT effects as Field, Duka et al. (2007) found effects on craving only for those participants who had been aware of this division during the training. Field and Eastwood (2005) did not find effects of awareness. Other studies did not have enough participants to perform separate analyses on contingency awareness (Chapter 4; Field et al., under review).

For a test of the causality of attentional bias a lack of awareness of the experimental hypotheses is of course important, as the findings could otherwise be attributed to demand effects. In studies that have measured participants' awareness, either no participants reported any awareness (Chapter 4), or participants' beliefs about the experimental hypotheses did not influence results (Field, Duka et al., 2007). There are few reports of the awareness of experimental hypothesis in addition to awareness of probe division. hen an AMT is designed as a clinical instrument (avoid-AMT, or attentional re-training), perhaps informing participants about the experimental contingencies is inevitable. In the three clinical studies (Fadardi & Cox, 2007 study 1 and 2; Chapter 5) participants were informed about the experimental contingencies in order to be able to explicitly support participants in improving their ability to avoid alcohol-related cues. Further, knowledge about uncontrolled appetitive processes may be important for patients in order to deal with these processes. Finally, during repeated training sessions, it is very likely that patients become aware of the contingencies sooner or later. For an experimental test of the avoid-AMT intervention, it is better to make all patients aware at the same time, instead of having them find out at different moments.

Measuring craving

Craving has mostly been measured with questionnaires directly after the AMT. In the reviewed studies with attend and avoid trainings, differential effects on craving have been restricted to the attend-AMT groups (Field, Duka et al., 2007; Field & Eastwood, 2005). A possible explanation for these increases in craving is priming; during the attend-AMT, participants are primed with substance-related stimuli resulting in alcohol cue effects (for a review on cue effects see Field, Schoenmakers & Wiers, 2008). I believe that craving should be measured after exposure to a situation in which attentional bias would lead to increased craving. That is, a situation in which someone with attentional bias is exposed to substance-related stimuli and will thereby experience cue-reactivity. In the same situation, someone who has learned to avoid substance-related stimuli will be less exposed to those stimuli and experience less cue-reactivity. A decrease in attentional bias after avoid-AMT results in less craving than an increase in attentional bias after attend-AMT. After an avoid-AMT,

substance-related stimuli will be attended to less (i.e. less cue exposure), and as a result craving will be triggered less.

This reasoning is in accordance with the MacLeod et al. (2002) study. In this study it was shown that participants were affected less by a stress-inducing task after avoid-AMT compared to attend-AMT. Also, a recent AMT study demonstrated that conscious emotional state was not affected by an AMT, but behaviour and preferences for appetitive stimuli were affected by AMT (Goetz, Robinson, & Meier, 2008). Thus an avoid-AMT may not directly affect subjective craving, but it does decrease one's vulnerability in a craving-triggering situation. This explanation accounts for the effects reported in Chapter 5, where no effect on craving was found after the training, but where effects on measures related to the vulnerability for alcohol cues were found. To measure vulnerability or indirect effects on craving, one could think of exposing participants to a craving-triggering video, or measure the amount of craving-episodes that participants experience during a specified period after avoid-AMT.

Underlying Mechanisms Avoid-AMT

Although only a few studies have found clinically relevant effects of avoid-AMTs, the few reports of repeated AMT sessions all indicate some changes in addiction (Fadardi & Cox, 2007; Chapter 5) and in anxiety (Mathews & MacLeod, 2002). The next paragraph deals with the underlying mechanism of the avoid-AMTs in their present form. These have received little attention in the literature. I will propose a model that explains the findings, and I will make suggestions on how to test the different aspects of the model (Figure 6.1). The general idea is that by a reduction in attentional bias, subsequent related addiction-relevant factors will be reduced as well. But how is attentional bias reduced exactly? Does the training reduce the appetitive value of substance-related stimuli? Is it possible to convert uncontrolled attentional approach into uncontrolled or automatic avoidance of substance-related stimuli?

The most obvious explanation for avoid-AMT effects is that by repeated practice (training) an avoidance reaction to substance-related stimuli is automated, which I label the 'automatic-avoidance learning' explanation. I will, however, discuss a different

explanation where the avoid-AMT effect is caused by controlled, not reflexive, responses away from substance-related stimuli. This avoidance will then lead to a devaluation of substance-related stimuli and interrupt appetitive processes that are normally evoked by attentional bias.

In the two clinical repeated-sessions AMTs (Chapter 5; Fadardi & Cox, 2007), participants are trained to gain control over their automatic attentional processes toward alcohol-related stimuli. Initially, they do not learn to automatically avoid addiction-related stimuli but rather to control their attention toward alcohol-related cues, which gives them the ability to disengage their attention from substance-related stimuli when they feel it is needed. Attentional bias is present in some situations but absent in others, for example in treatments where no alcohol is available (cf. Wilson, Sayette, & Fiez, 2004). Increased control over one's attention for alcohol-related cues becomes relevant when attentional bias does emerge. I believe this 'substance-specific attentional control' explanation is more likely than the automatic-avoidance explanation, at least for addiction since no effects of avoid-AMT have yet been found on early stages of attentional processing.

We found no effect of avoid-training on the speeded detection of alcohol-related cues, but only on the delayed disengagement (Chapter 5). This indicates that a controlled, delayed avoidance (i.e. disengagement) is possible but automatic, instant avoidance is not, at least not with the visual-probe AMT in its present form. Likewise, in anxiety, Koster (2008) and MacLeod et al. (2002) also found that AMT only affected later stages of attentional processing, but not earlier stages. In contrast, also in anxiety, Mathews and Macleod (2002) did find a decrease in early detection in anxiety after repeated avoid training sessions. Unfortunately, they did not report pre-test attentional bias scores. Possibly, speeded detection can be reduced to zero, i.e. equal response latencies for congruent and incongruent trials, but not be further reduced to avoidance, i.e. shorter response latencies for incongruent than for congruent trials. Patients in our clinical study showed no overall attentional bias at pre-test for speeded detection (Chapter 5). Perhaps it could not be further reduced to avoidance.

Another possibility is that avoid-AMT improves general executive attentional control. Improvement in training performance in a domain where one particularly experiences difficulties with attentional control could require employing attentional functioning at a

higher, more general level. Consequently, general attentional control is practiced during AMT. Mainly at later stages of processing, attentional bias can be influenced by attentional control (Derryberry & Reed, 2002). Improvement in executive attentional control then has a dampening effect on appetitive motivational responses, since low levels of control increase automatic appetitive motivational processes.

This idea can be explained as follows: addiction is characterized by impaired executive functioning or inhibitory control (Jentsch & Taylor, 1999; Wiers, Bartholow et al., 2007), leading to an increase in uncontrolled cue-driven behaviour. For example, impulsive decision making has been found to be positively related to attentional bias in heavy social drinkers (Field, Christiansen, Cole, & Goudie, 2007). Further, automatic appetitive motivation (implicit positive arousal associations) predicted drinking behaviour at one month follow up more strongly in at-risk adolescents with poor than better working memory capacity (Thush et al., 2008). The ability to control attention is a chief contributor to working memory capacity (Barrett, Tugade, & Engle, 2004). An improvement in executive attentional functioning might then enhance the ability to decrease this cue-driven behaviour and attentional bias.

When participants are made aware of attentional bias or other uncontrolled appetitive processes, and they are motivated to reduce them, improved executive attentional functioning can help them to overcome these processes. This possibility can be tested by including a dependent measure of general attentional functioning in a study on AMT. Vice versa, if this explanation is correct, a training that directly targets general attentional control is also effective in reducing automatic appetitive responses such as attentional bias.

A possible consequence of controlled, intentional avoidance is that the stimuli that are avoided will be devaluated. Studies using facial stimuli (Raymond, Fenske, & Westoby, 2005) and abstract stimuli (Raymond, Fenske, & Tavassoli, 2003) indicate that deliberately ignoring stimuli leads to the devaluation of these stimuli, and that the degree of stimulus devaluation is related to the degree of efficiency in attentional selecting (Kiss et al., 2007). Vice versa, when the valence of a stimulus is decreased, it might become easier to withdraw attention from the stimulus. Although according to the incentive sensitization theory drug "liking" becomes less relevant for predicting drug abuse, it could still have an effect on appetitive processes. For example, Field, Mogg, Zetteler et al. (2004) found that heavy

drinkers could be discriminated on attentional bias from light drinkers, and heavy drinkers rated alcohol-related stimuli as more pleasant. Bradley, Field, Healy, and Mogg (2008) found that in smokers the affective properties of smoking-related cues were related to approach tendencies. In our study in which avoidance was effectively trained, participants were instructed to avoid alcohol-related stimuli (Chapter 5). They deliberately ignored stimuli, which inhibited their reaction toward the stimuli during the training. Whether this leads to stimulus devaluation can be tested by including stimulus evaluation measures before and after an avoid-AMT.

Another consequence of stimulus avoidance may be that the incentive motivational process of drug pursuit is interrupted. The Incentive Sensitization theory states that drug-related stimuli become hypersensitized after a long period of repeated use (Robinson & Berridge, 1993, 2001). This leads to increased salience of these cues, which makes them more attracting, 'grab the attention', and more 'wanted', leading to approach tendencies and drug pursuit. This process is said to occur automatically, without awareness. When the process comes into awareness, subjective craving for the drug is felt (Tiffany, 1990). This implies that approach tendencies occur automatically and very quickly, and subjective craving occurs only later. Training addicts to avoid addiction-related stimuli might prevent 'wanting' to come into awareness. Thus the incentive motivational process of drug pursuit is stopped by quickly avoiding addiction-related cues and focusing at other, neutral, cues. Consequently, avoid-AMT does not directly stop incentive salience processes, but rather stops reinforcing it by preventing craving and consequent drug use to emerge.

The explanations as outlined above (attentional control, stimulus-devaluation and process-interrupting) can be integrated in a model underlying the clinically relevant effects after avoid-AMT (see Figure 6.1, p. 134). The model proposes that the effect of avoid-AMT on attentional avoidance is influenced by increased attentional control. Attentional control either refers to control over attention for substance-related cues, general attentional functioning, or both. Selective avoidance of/disengagement from substance-related cues is initially a controlled process leading to devaluation of substance-related cues. Later on, after repeated practice, this avoidance becomes automated. This automated avoidance should not be confused with avoidance in early attentional processing (i.e. initial or speeded avoidance), but is rather a disengagement from substance-related stimuli after

attention was initially drawn toward these stimuli. Further, a consequence of avoidance is a decrease in exposure. This refers to decreased exposure during the training, but also decreased exposure in real life when cues are effectively less attended to.

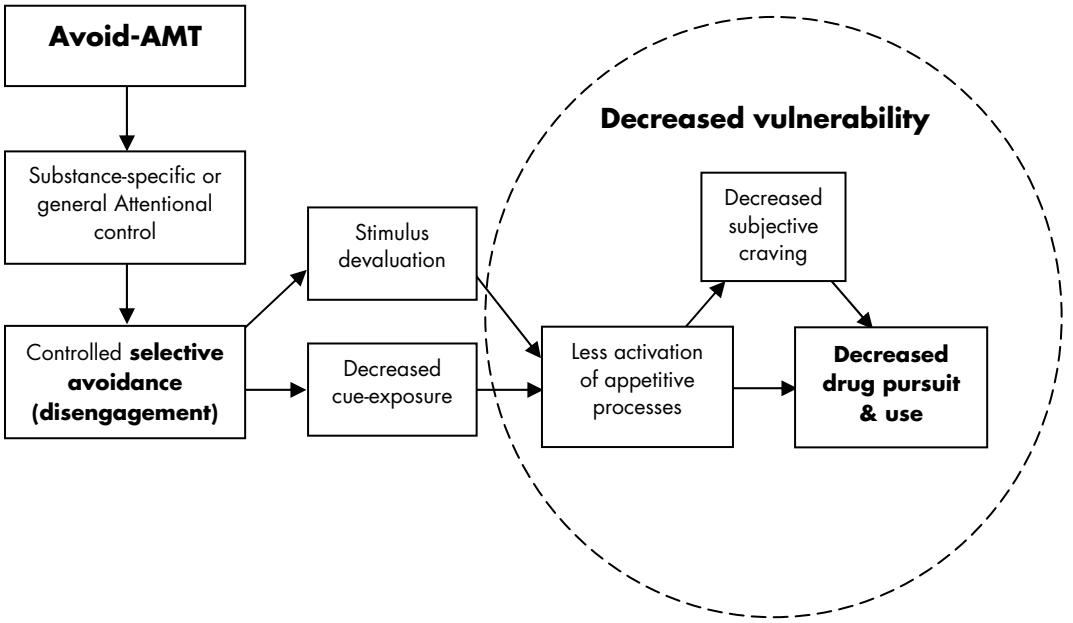
The crucial effect of stimulus devaluation and decreased cue-exposure is the decease in vulnerability for addiction-related cues. Vulnerability is decreased because appetitive motivational processes (i.e. implicit associations, approach bias and attentional bias) are interrupted when attention is disengaged from substance-related cues. Clinically relevant decreases in vulnerability can be measured by decreases in negative consequences related to attentional bias, such as rumination resulting from cue exposure, relapse and craving episodes. Central to the model is the effect of avoid-AMT on decreased selective attention for substance-related cues. Therefore, a possible moderating influence of improved general attentional or cognitive functioning on the relationship between implicit appetitive processes, craving and behaviour is not further specified in Figure 6.1. But it is very likely that the inhibition of behavioural responses as a result of appetitive approach processes is enhanced by improved cognitive control.

Implications derived from the model

According to the model, avoid-AMT has several advantages as a clinical tool. Firstly, if it increases the ability to control attention, then it might easily generalize to different environments and not be restricted to the training setting. A reason why substance-cue based treatment, such as cue exposure therapy, does not easily generalize to new environments, is that it focuses on associations. The problem is that in every other environment, different cues might activate existing associations that steer drug use (Conklin & Tiffany, 2002; Gawronski & Bodenhausen, 2006). According to the avoid-AMT model, avoid-AMT increases the ability or skill to control attention and subsequent exposure which could probably be exerted in different situations; AMT does not directly change underlying associative impulsive processes, but the ability to control the process that further activates those cognitions. To test this generalizability, one could expose trained subjects to different situations that can trigger craving-like responses. For example,

one could measure participants' craving after exposure to a video with substance-related cues. I would expect that participants who are motivated to reduce their drinking and are aware of the risk of attentional bias will try to avoid these cues. An effectively trained participant will selectively avoid those stimuli and subjective craving will not occur.

Figure 6.1
Avoid-AMT mechanisms.



Another advantage is that attentional bias needs not necessarily be present during avoid-AMT; increased control over attention for addiction-related stimuli and stimulus devaluation will occur anyway. Avoid-AMT could be effective in addicts who show no attentional bias at the time of testing (see Noël et al., 2006; Townshend & Duka, 2007), but who *are* prone to show attentional bias in high-risk situations, for example when their substance of abuse is at hand.

A disadvantage of the visual-probe AMTs is that they are probably not very influential at early stages of attentional processing. There is, however, some evidence for early processing of alcohol-related stimuli in inpatient alcoholics (Ingjaldsson, Thayer, & Laberg, 2003a, 2003b; Noël et al., 2006; Stormark et al., 1997). Additionally, in social drinkers, early processing increased after a low dose of alcohol (Chapter 3). This means that first of all, experimental research should demonstrate that these early processes are important in the development or maintenance of addiction. Therefore, a different manipulation should be designed that is able to influence early processing. Secondly, such a manipulation can subsequently be probed as a training to reduce early processing of substance-related stimuli.

General conclusion and clinical implications

Based on the research in this thesis and the research that has been conducted by others, we may carefully conclude that attentional bias is causally related to the aggravation and maintenance of addictive behaviours. We have seen that alcohol use is affected by alcohol cues and alcohol prime doses and we should bear in mind that this could have an accumulating effect on alcohol consumption. Further, there have been a number of studies relating attentional bias to craving (e.g. Noël et al., 2006), drinking (e.g. Fadardi & Cox, 2008), and relapse (e.g. Cox et al., 2002; Marissen et al., 2006), although experimental tests of the relationship are scarce and results are mixed (compare Field & Eastwood, 2005, to Field, Duka et al., 2007; see also MacLeod et al., 2002, vs. Harris & Menzies, 1998). Notwithstanding these mixed results, most publications on investigations of clinical interventions on attentional bias have shown positive effects of attention modification

training on clinical outcome measures for anxiety (Mathews & MacLeod, 2002), self-esteem and social-threat (Dandeneau & Baldwin, 2004; Dandeneau et al., 2007), and alcohol abuse (Chapter 5; Fadardi & Cox, 2007).

At present, many treatments target false or harmful beliefs, expectancies, and behaviour, either directly by counseling or indirectly by behavioural therapy. Besides, patients are often given medication to prevent craving or positive outcomes from drinking. In addition to those treatments, I would suggest that patients - and their therapists - are educated in more automatic, uncontrolled, implicit processes that underlie addiction. They should know that these processes can steer their behaviour, and that this influence likely increases when they are confronted with alcohol cues or when they drink alcohol. Interventions such as the avoid-attention modification training or perhaps more general cognitive or attentional control exercises then could be administered to increase control over these implicit processes and perhaps to decrease their detrimental effects on behaviour enduringly.

SUMMARY

Recent models of addiction distinguish between two types of cognition that influence substance use and abuse: explicit and implicit cognitions. These cognitions influence appetitive motivation, which is the drive to approach and pursue appetitive substances such as drugs and alcohol. Explicit cognitions can be measured with questionnaires; roughly stated, these are reports of feelings or thoughts, such as beliefs about the reasons for using an addictive substance ("Does drinking alcohol reduce your worries?"), or one's present state ("How much do you crave alcohol right now?"). Implicit cognitive processes are often measured with reaction time tasks. They are not always accessible to peoples' awareness, may operate automatically, and are difficult to control. Central to this thesis is the implicit process 'attentional bias', defined as an excessive selective attention for substance-related cues. This selective attention is related to the maintenance and development of addictive behaviours.

In general, the thesis deals with changing implicit processes that underlie the appetitive motivation for substance use and abuse. More specifically, the first studies of the thesis (Chapters 2 and 3) were aimed at broadening the knowledge on the effects of alcohol consumption (i.e. alcohol prime dose effects) on various aspects of appetitive motivation: attentional bias, eye movements, approach bias and craving. The second line of research (see Chapters 4 and 5) focused on a training method to decrease attentional bias and related clinical factors.

In the study described in Chapter 2, we found that the maintenance of attention, the gaze dwell time and number of first eye movements toward alcohol-related stimuli were all increased after consumption of a low dose of alcohol compared to after a placebo drink. This alcohol dose was adjusted for body weight and was equal to three Dutch standard units of alcohol for someone weighing 80 kg. Unexpectedly, there was no larger approach bias after the low alcohol dose. We did, however, measure an increase in subjective craving after alcohol that was not found after a placebo drink. Overall, this suggests an increase in appetitive motivation for alcohol after a low prime dose of alcohol. Additionally, attentional bias and approach bias were correlated much higher after the prime dose than after the placebo. Possibly, the latter finding is caused by decreased inhibitory control over automatic processes after alcohol consumption. When implicit appetitive tendencies are

not affected by effortful control they might better reflect their mutual underlying construct, appetitive motivation.

In a second study on alcohol prime effects (Chapter 3), we measured appetitive motivational constructs following alcohol consumption in a real-life setting. Lab studies had shown changes in craving and attentional bias after prime doses. However, no research had been conducted that tested whether these effects could also be measured in a real-life setting, and to what extend these changes relate to alcohol-consumption levels in real-life. We tested an opportunistic sample of social drinkers in a pub. Controlling for usual drinking behaviour, we found increases in craving up to very high alcohol doses. We did not find a significant relation between attentional bias and alcohol consumption in participants who had been drinking less than a binge at the time of testing (less than 6 drinks for males, less than 5 drinks for females). However, for people who had been bingeing attentional bias was negatively correlated with the amount of alcohol consumed. The results indicate that different aspects of appetitive motivation respond differently to alcohol priming and subsequently, they might affect alcohol consumption in a different way.

The second line of research of this thesis focused on a training method to decrease attentional bias. If proved to be effective, such a method might eventually be used as a clinical tool. In this computerized training, participants are trained to avoid alcohol-related stimuli; it is therefore also called 'avoid-attention modification training' (avoid-AMT). In a first study in the lab with male heavy drinkers (Chapter 4), attentional bias decreased after the avoid-AMT, but only for the specific stimuli that were used in the training. There were no effects on untrained stimuli and no effects on a second measure of attentional bias. Also, craving and drink preference were not affected by the training. Thus our first avoid-AMT did not reveal clinically relevant effects, nor did it show evidence for a causal relation between attentional bias and craving - as would have been the case when the manipulation/training of attentional bias had resulted in a contingent craving effect.

We figured that by increasing the intensity of the avoid-AMT (by increasing the number of training stimuli and sessions, and by motivating participants to perform better), a stronger effect may be obtained. In the second avoid-AMT study (Chapter 5), we trained alcoholic patients of three clinics in five sessions. This intervention was successful in

decreasing attentional bias for trained and untrained stimuli, indicating that attention for the complete category of alcohol-related stimuli had been changed. Patients reported little craving at all at pre-test which might explain why we did not find decreased craving after the intervention. In the clinic with the shortest regular treatment program, patients in the avoid-AMT group were much sooner discharged than patients in the control group, suggesting that the training had a positive effect on the regular treatment program that was mainly focused on cognitive behavioural therapy. Finally, of the few patients who relapsed after the treatment program, patients in the re-training group relapsed at a later time than patients of the control group, indicating that the training had a positive effect on time to relapse.

In the general discussion of this thesis (Chapter 6), I have reviewed avoid-AMT studies that had been published at the time of writing. At the end of the review I have proposed a model to explain clinical effects of avoid-AMT. The model predicts that the effect of avoid-AMT on attentional bias is influenced by increased control over attention for substance-related cues, general attentional functioning, or both. Selective avoidance of / disengagement from substance-related cues is initially a controlled process. Later on, after repeated practice, this avoidance might become automated. The crucial effect of decreased attentional bias after an avoid-AMT intervention is the decrease in vulnerability for addiction-related cues. Interventions such as the avoid-AMT or perhaps more general attentional control exercises could be administered to increase control over implicit addiction-related processes and perhaps to decrease their detrimental effects on behaviour enduringly.

SAMENVATTING

Recente verslavingstheorieën onderscheiden twee manieren waarop onze hersenen met informatie omgaan: impliciet en expliciet. Deze vormen van informatieverwerking (*cognitie*) beïnvloeden de motivatie om verslavende middelen te gebruiken: dit noemen we appetitieve motivatie. *Expliciete cognities* zijn gedachten waar je iemand naar kunt vragen, dus daarbij ga je ervan uit dat iemand inzicht heeft in zijn of haar redenen om te gebruiken. Dit zijn bijvoorbeeld overwegingen die mensen maken om een middel wel of niet te gebruiken ("Alcoholgebruik vermindert mijn dagelijkse zorgen"). Maar expliciete cognities gaan ook over hoe iemand zijn huidige gemoedstoestand waarneemt ("Op dit moment heb ik erg veel trek in een glas alcohol"). *Impliciete cognities* bestaan vaak zonder dat mensen zich ervan bewust zijn. Ze worden automatisch geactiveerd bij het waarnemen van bepaalde stimuli (voorwerpen, mensen, woorden, gebeurtenissen), doordat mensen associaties hebben gemaakt met die stimuli. Door die automatische activatie zijn ze moeilijk onder controle te houden. Zo kan het zien van een glas wijn er voor zorgen dat je er een slok van neemt zonder daar over na te denken. Impliciete cognities worden niet met vragenlijsten gemeten maar met computertaken waarin iemands reactie op stimuli gemeten wordt.

Een impliciete vorm van cognitie dat in dit proefschrift centraal staat is *aandachtsbias*. Dit kan gedefinieerd worden als een overmatige selectieve aandacht voor drug-gerelateerde voorwerpen ("cues" of "stimuli"). De aandacht van zware alcoholdrinkers gaat bijvoorbeeld automatisch richting alcoholgerelateerde voorwerpen en blijft daarop hangen. Dit komt doordat een alcoholvoorwerp het beloningssysteem in de hersenen activeert, en mensen focussen automatisch op dingen met een belonende waarde. Verschillende theorieën voorspellen dat door de focus op alcoholvoorwerpen de drang om te drinken toeneemt waardoor mensen meer gaan drinken, of opnieuw gaan drinken na een periode van onthouding. Aandachtsbias is hierdoor gerelateerd aan het in stand houden en de ontwikkeling van verslaving.

In het algemeen gaat het proefschrift over het veranderen van impliciete processen die ten grondslag liggen aan de appetitieve motivatie voor middelengebruik en -misbruik. De eerste onderzoeken in het proefschrift (Hoofdstukken 2 en 3) waren gericht op het vergroten van wetenschappelijke kennis over effecten van alcoholconsumptie op verschillende aspecten van appetitieve motivatie (de motivatie om te drinken), namelijk

aandachtsbias, oogbewegingen, toenaderingsbias (een lichamelijke reactie richting een alcohol voorwerp) en verlangen naar alcohol ("craving"). De onderzoeken in het tweede gedeelte van het proefschrift (Hoofdstukken 4 en 5) waren gericht op een training om aandachtsbias te verminderen en te kijken of daarmee ook andere klinische symptomen (zoals verlangen naar alcohol, en terugval na behandeling) zouden verminderen.

In het onderzoek uit Hoofdstuk 2 gaven we proefpersonen in één sessie een alcoholische drank (een kleine hoeveelheid alcohol), en in een andere sessie een drankje zonder alcohol met dezelfde smaak (placebo). Vervolgens kregen de proefpersonen een computertaak waarin hun aandachtsbias gemeten werd. In deze taak (de visuele probe taak) verschenen twee stimuli telkens tegelijkertijd in beeld: een plaatje van een alcoholvoorwerp (bijvoorbeeld een fles wijn) en een plaatje van een neutraal voorwerp (bijvoorbeeld een fles water). Na het drinken van alcohol hadden de proefpersonen meer aandacht voor alcoholvoorwerpen in de computertaak dan voor de neutrale voorwerpen; dit was niet het geval na het drinken van de placebo. Dat zagen we omdat na het drinken van alcohol de ogen langer gefixeerd waren op alcoholvoorwerpen dan op neutrale voorwerpen, en omdat zodra de plaatjes in beeld kwamen, de eerste oogbeweging in de meeste gevallen richting het alcoholplaatje ging. We verwachtten ook dat de toenaderingsbias (ook met een computertaak gemeten) toe zou nemen na het drinken van alcohol, maar dit gebeurde niet. Het verlangen naar alcohol nam wel toe. Al met al suggereren deze bevindingen dat appetitieve motivatie voor alcohol toeneemt na een kleine alcoholinname. Daarnaast vonden we dat aandachtsbias en toenaderingsbias veel sterker met elkaar samenhingen na het drinken van alcohol. Wellicht is dit te verklaren door een afname in controle over impliciete/automatische processen door de effecten van alcohol. Als controle namelijk minder wordt na het drinken van alcohol (de rem gaat eraf bij wijze van spreken), dan worden de impliciete processen beter gemeten en zouden ze meer met elkaar samen moeten hangen. Wanneer je bij verschillende computertaken op verschillende manieren controle uitoefent op impliciete processen worden deze elk op verschillende wijze verstoord en zullen ze minder op elkaar lijken.

In een tweede onderzoek naar de effecten van alcoholconsumptie (Hoofdstuk 3) meetten we appetititive motivationele processen niet in het lab, maar in de kroeg: in het echte leven. Verschillende lab studies hadden al veranderingen in verlangen naar alcohol

en aandachtsbias laten zien na een dosis alcohol. Er was echter nog geen onderzoek verricht naar deze effecten buiten het lab. Zo wisten we nog niet in welke mate deze veranderingen samenhangen met de hoeveelheid gedronken alcohol in werkelijkheid. In twee kroegen, in Maastricht en Sittard, testten we mensen die daar aan het drinken waren. We vonden dat het verlangen naar alcohol toenam tot erg hoge doses alcohol, ook als we statistisch rekening hielden met de hoeveelheid die de mensen gewend waren te drinken. Bij de mensen die nog geen *binge*-hoeveelheid hadden gedronken (mannen minder dan 6 glazen, vrouwen minder dan 5) was er geen relatie tussen de hoeveelheid gedronken alcohol en aandachtsbias. Bij de groep mensen die al wel een *binge* (of meer) gedronken hadden was er wel een relatie: aandachtsbias nam af naarmate de hoeveelheid gedronken alcohol toenam. Deze resultaten en die van de labstudie laten zien dat verschillende aspecten van appetitieve motivatie verschillend kunnen reageren op alcohol consumptie, en dat ze wellicht ook de consumptie van alcohol op een verschillende manier beïnvloeden. Zo lijkt aandachtsbias bij een kleine hoeveelheid alcohol toe te nemen en bij een grote hoeveelheid weer af te nemen. Het verlangen naar alcohol daarentegen neemt toe zolang iemand blijft drinken.

De tweede onderzoekslijn in dit proefschrift gaat over een training om aandachtsbias te verminderen. Wanneer deze aandachtstraining effectief zou blijken zou die uiteindelijk gebruikt kunnen worden als behandelmethode binnen de verslavingszorg. De aandachtstraining is een computertaak waarin deelnemers worden getraind om hun aandacht van alcohol gerelateerde stimuli (plaatjes) af te halen. In een labstudie met mannelijke zware drinkers (Hoofdstuk 4) nam aandachtsbias af na de training. Dit was echter alleen de aandacht voor plaatjes die in de training gebruikt waren. Er waren geen effecten op plaatjes waarmee niet getraind was en ook niet wanneer de aandacht met een andere test gemeten werd. Ook verlangen naar alcohol en voorkeur voor alcohol of frisdrank veranderde niet door de training. Dus onze eerste test van de aandachtstraining leidde niet tot gewenste klinisch relevante effecten (op verlangen en drinkgedrag).

We bedachten dat we een sterker effect van de training zouden krijgen wanneer we deze zouden intensiveren: door meerdere stimuli in de training te gebruiken, meerdere trainingsessies te laten doen, en door deelnemers te motiveren om beter te gaan presteren in de training. In het tweede onderzoek naar de aandachtstraining (Hoofdstuk 5)

trainden we in vijf sessies alcoholverslaafde patiënten uit drie verslavingsklinieken. Na deze intensieve trainingsinterventie nam aandachtsbias voor zowel plaatjes uit de training als nieuwe plaatjes af; dit bewijst dat door de training de aandachtsbias voor alle alcohol gerelateerde voorwerpen kan afnemen, en niet alleen voor plaatjes die in de training gebruikt waren. We vonden ook in deze studie geen afname in verlangen naar alcohol. Dit zou echter verklaard kunnen worden doordat de patiënten op de voormeting al aangaven nauwelijks verlangen naar alcohol te hebben. In de kliniek met de kortste standaard behandeling (3 maanden cognitieve gedragstherapie) werden deelnemers uit de trainingsgroep veel sneller met positief advies ontslagen door hun behandelaar dan patiënten uit een controle groep. Dit geeft aan dat de training waarschijnlijk een positief effect had op het standaard behandelprogramma. Tot slot, van de weinige patiënten die terugvielen in alcoholmisbruik na de trainingsinterventie vielen de deelnemers uit de trainingsgroep later terug dan deelnemers uit de controle groep, een aanwijzing dat de training een vertragend effect op terugval heeft.

In de algemene discussie van het proefschrift (Hoofdstuk 6) heb ik alle aandachtstrainingstudies beschreven en onderzocht die tot het moment van schrijven gepubliceerd waren. Aan het eind van dat hoofdstuk heb ik een model voorgesteld dat de klinische effecten van aandachtstrainingen verklaart. Het model voorspelt dat het effect van aandachtstraining op aandachsbias wordt beïnvloed door toegenomen controle over aandacht voor verslavingsgerelateerde voorwerpen, of door een toename in een algemene controle over aandacht, of door beide. De selectieve vermijding (afgenomen aandacht) van verslavingsgerelateerde voorwerpen, die optreedt na de training, gebeurt dus allereerst gecontroleerd en niet automatisch. Later, na herhaalde oefening zou het vermijden automatisch kunnen gaan. Het cruciale effect van een afgenomen aandachtsbias is de afname in kwetsbaarheid voor verslavingsgerelateerde voorwerpen. Dat houdt in dat de kans op middelenmisbruik en terugval door blootstelling aan deze voorwerpen kleiner is geworden. Interventies zoals de aandachsttraining of wellicht ook meer algemene aandachtscontrole-oefeningen zouden toegepast kunnen worden om de controle over impliciete verslavende processen te versterken, en wellicht daarmee hun schadelijke effecten op gedrag blijvend te verminderen.

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CURRICULUM VITAE

Tim Schoenmakers was born on 22 February 1980 in Breda, The Netherlands. In 1998 he graduated from secondary school, Stedelijk Gymnasium Breda. In 2003 he obtained his Master's degree in Communication Science at the University of Amsterdam, with a specialization in commercial advertising and public campaigns. At the same university he obtained a minor in Social Psychology in 2002. Between 2004 and 2008 he worked on his PhD project at Maastricht University, department of Clinical Psychological Science. He conducted part of this project at the University of Liverpool, School of Psychology. Since September 2008 he is working as a research coordinator at IVO in Rotterdam.

Publications

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Invited presentations

Graduiertenkolleg Emotions, University of Würtzburg, Germany (2009)
Wageningen University, Netherlands (2008)
European Society for Biomedical Research on Alcoholism, Berlin, Germany (2007)
Research Society on Alcoholism, Chicago, USA (2007)

Vereniging voor Gedragstherapie en Cognitieve Therapie, Netherlands (2007)
Riagg Maastricht, Netherlands (2007)
Mondriaan Zorggroep, Heerlen, Netherlands (2007)
Iriszorg, Arnhem, Netherlands (2007)
Onderzoeksschool Experimentele Psychopathologie, Netherlands (2006)
Research Society on Alcoholism, Santa Barbara, USA (2005)
Cultuur- en Maatschappijwetenschappen, Maastricht University, Netherlands (2005, 2006, 2007)