

Exploring factors related to craving and relapse in alcohol-dependent outpatients

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Exploring factors related to craving and relapse in alcohol-dependent outpatients

Verkenning van factoren gerelateerd aan trek en terugval bij
ambulante alcoholverslaafde patiënten

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Chapter 1: General introduction

General Introduction

Alcohol use and dependence is still a worldwide problem. In 2012, 5.9% of all global deaths (3.3 million deaths) were attributable to alcohol consumption and 5.1% of the global burden of disease and injury were attributable to alcohol consumption (World Health Organisation, 2014). In 2011, 66.000 new cases of alcohol abuse and 15.300 new cases of alcohol dependence were reported in the Netherlands (de Graaf, Tuithof, & Dorsselaer, 2012).

Alcohol dependence is characterized by tolerance for alcohol, withdrawal symptoms, loss of control over alcohol use, and difficulties at work, at school, or at home because of using or obtaining alcohol (de Bruijn, van den Brink, de Graaf, & Vollebergh, 2006). These problems tend to diminish or disappear when these individuals become abstinent.

Unfortunately, many alcohol-dependent patients relapse during or after treatment even though many improvements have been made in the treatment for alcohol-dependence, for example by incorporating relapse prevention as a component of most treatment manuals (Boothby & Doering, 2005; Finney, Hahn, & Moos, 1996; Witkiewitz & Marlatt, 2007). Even though most alcohol-dependent patients become abstinent or learn to control their drinking during treatment, many of these patients will eventually still relapse (Witkiewitz & Marlatt, 2007). Therefore, much research has been conducted on possible determinants of relapse. Some of these studies investigated one single determinant while other studies examined the interplay of various possible determinants of relapse.

This research has resulted in the development of various theoretical models of relapse. One of these models is the dynamic model of relapse (Witkiewitz & Marlatt, 2004). This model, displayed in Figure 1, states that various factors elevate the risk of relapse in high-risk situations and relapse is due to the interaction between determinants. The model distinguishes between tonic processes and phasic responses. Tonic processes, which determine the individual's chronic vulnerability to relapse, include cognitive processes, physical withdrawal states, and distal risks such as family history of dependence. These tonic processes often accumulate and lead to the instigation of a high-risk situation, providing the foundation for the possibility of a relapse. In the dynamic model, the phasic response is the critical point at which affective states or coping behaviors influence substance-using behavior. In this thesis we will focus on the proximal risks such as affect and

implicit cognitive processes, not on the distal risks such as family history or social support.

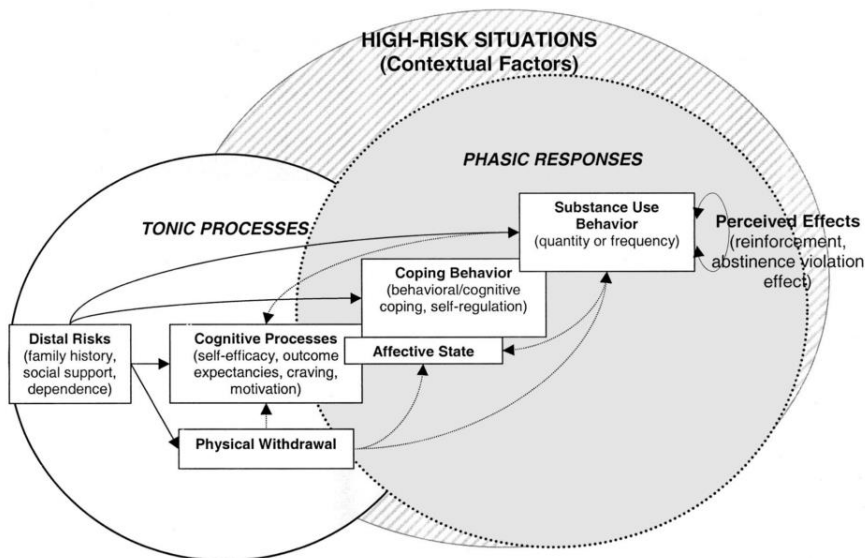


Figure 1. Dynamic model of relapse, reprinted from Witkiewitz and Marlatt (2004, p. 230)

In addition, this thesis will also focus on the role and determinants of craving. The main reason to explore role and the determinants of craving is that there is still debate on whether craving is an important determinant of relapse. For example, Holt et al. (2012) found that craving did not predict subsequent relapse in alcohol-dependent patients undergoing treatment while other studies did find that craving does predict relapse in alcohol-dependent patients (Higley et al., 2011; Miller, Westerberg, Harris, & Tonigan, 1996) while all of the patients in these studies experienced craving. This could mean two things: (1) craving may be absent when a relapse occurs, and (2) craving may occur without instigating a relapse. Since the experience of craving can be very intrusive and interferes in daily life (Tiffany & Wray, 2012) and knowing what may cause craving may aid in improving treatment components that focus on craving, it is important to study the determinants of craving as well.

Another reason to explore craving determinants is that: (a) the experience of craving can be very intrusive and interferes in daily life (Tiffany

& Wray, 2012) and knowing what may cause craving may aid in improving treatment components that focus on craving, and (b) recently craving has been added as a symptom for the diagnosis of alcohol-dependence in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013), making it even more important to know what triggers craving.

The overall aim of this thesis is to explore proximal determinants of relapse and craving in abstinent alcohol-dependent outpatients. More specifically, this thesis aims to compare the determinants of craving and relapse, and investigates further if craving is a predictor of relapse in alcohol-dependent outpatients.

Determinants of relapse

Much research has been conducted on predictors of relapse and focused on personality variables such as impulsivity and trait anxiety, which are seen as stable traits (Willinger et al., 2002). Additionally, more transient negative emotional states, in particular state anxiety and stress are argued as being the main predictors of relapse (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Brady & Sonne, 1999; Marlatt & Donovan, 2005). The determinants under investigation in this thesis will be discussed in more detail below.

Negative affect

As discussed, negative affect is argued as being one of the main predictors of relapse. In addition, various theoretical models describe that negative affect is an important factor in establishing and maintaining dependence for alcohol. Some of these models posit that negative affect is also a predictor of relapse. For example, the Affective Processing Model of Negative Reinforcement (Baker et al., 2004) states that stressors cause or increase negative affect, which in turn activates the learned rewarding properties of alcohol (or other addictive substances) that relieve negative affect, thereby motivating the individual to use again. Alcohol-dependent individuals have learned that alcohol relieves negative affect through past experiences. Through repeated use in negative affect situations, associations are formed between alcohol use and relief of negative affect by means of negative reinforcement. As a consequence, alcohol use is provoked when alcohol-dependent individuals experience negative affect. Indeed, alcohol-dependent patients often report that they drink to relieve

negative affect (Kushner, Thuras, Abrams, Brekke, & Stritar, 2001). In addition, it is suggested that targeting the relationship between negative affect and alcohol use could greatly decrease the probability of relapse (Witkiewitz & Villarroel, 2009) because negative affect is predictive of relapse (Walitzer & Dearing, 2006; Witkiewitz & Villarroel, 2009).

Alcohol-related cues

Another factor contributing to increased risk for relapse is cue sensitivity. Hereby we mean that the brain is sensitive to alcohol-related cues, leading to a strong reaction towards these cues, i.e., cue reactivity. According to the Incentive Sensitization theory (Robinson & Berridge, 1993), specific cues (e.g., stimuli, situations) become associated with an addictive substance through repetitive use in the presence of these cues. The substance-related cues become attractive and therefore salient to the addict and activate a neurological hypersensitive reaction to a substance (Grüsser et al., 2004; Tapert et al., 2003). This hypersensitivity may remain even after long periods of abstinence (Koob & Le Moal, 2001; Robinson & Berridge, 2001). Because it is difficult to measure sensitivity for alcohol-related cues in the brain, researchers measure the response to those cues, i.e., cue reactivity. There are a number of ways to assess cue reactivity as proxy for cue sensitivity: physiological measures, subjective measures, behavioral measures, or a combination of these measures. Examples of physiological measures include heart rate or heart rate variability (HRV) and skin conductance (Carter & Tiffany, 1999; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Waters, Carter, et al., 2009). Cue sensitivity may also be measured subjectively and is often defined as increases in craving or the desire for alcohol after encountering alcohol-related cues (Bohn, Krahn, & Staehler, 1995; Schulze & Jones, 2000). Finally, another indicator of cue sensitivity is attentional bias, i.e., a selective focus on alcohol-related cues. Attentional bias is assessed with a reaction time task assessing the extent to which alcohol-related cues are selectively attended to as compared to neutral cues (Field & Cox, 2008).

Implicit processes

Over the past decades, addiction research has started to focus on relatively automatic cognitive processes as determinants of substance use (Tiffany, 1990; Wiers & Stacy, 2006). These processes - also called implicit cognitions- are provoked by substance related cues and can evoke behavior

without cognitive elaboration. Examples of these processes are attentional bias (AB; selective attention for cues) and approach/avoidance tendencies (AA; motor response toward or away from cues). After exposure to alcohol related cues, cognitive processes are spontaneously triggered and set into action motor responses to drink or activate feelings of craving for alcohol (Garland, Boettiger, & Howard, 2011). By now, a substantial number of studies have demonstrated a relationship between these implicit cognitive processes and substance use, abuse, and relapse (e.g., Cox, Hogan, Kristian, & Race, 2002; Field, Kiernan, Eastwood, & Child, 2008; Field, Mogg, & Bradley, 2005; Houben & Wiers, 2006; Marissen et al., 2006; Roefs et al., 2011; Schoenmakers et al., 2010; Waters, Shiffman, & Sayette, 2003; Wiers, Van Woerden, Smulders, & De Jong, 2002). On the other hand, some studies did not find a relationship between attentional bias and relapse (Field, Mogg, Mann, Bennett, & Bradley, 2013).

As stated before, attentional bias is a selective focus on alcohol-related cues and is measured using reaction time tasks. One often used task is the Addiction Stroop task (Cox, Fadardi, & Pothos, 2006) which measures interference for addiction-related, in this case alcohol-related, stimuli. This interference reflects how performance suffers from selective attention to the content (i.e. alcohol-related) of a stimulus that should be ignored during the task.

While attentional bias has received more attention in addiction research, there is also evidence that another implicit process might have a relationship with relapse in alcohol dependence. As mentioned before, approach/avoidance tendencies are motor responses which are triggered by alcohol-related stimuli. Evidence exists that alcohol-related stimuli can trigger approach tendencies in heavy drinkers (Field et al., 2008; Ostafin & Palfai, 2006; Palfai & Ostafin, 2003; Wiers, Rinck, Dictus, & van den Wildenberg, 2009). Additionally, there seems to be a positive association between pretreatment drinking levels and approach tendencies in recently detoxified alcohol-dependent patients (Barkby, Dickson, Roper, & Field, 2012). There is also evidence for a causal relationship between approach/avoidance tendencies: training abstinent alcohol-dependent patients to avoid alcohol-related stimuli has been shown to result in lower relapse rates (Eberl et al., 2013; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). In contrast, one study found that avoidance tendencies in abstinent alcohol-dependent patients predicted relapse within three months (Spruyt et al., 2013). In sum, results on the predictive value of

approach/avoidance tendencies for relapse remains unclear and will be investigated further in this thesis.

Craving

Despite the large body of research on craving, there is still debate on the definition of craving (Kozlowski & Wilkinson, 1987). For example, Marlatt and Donovan (2005) define craving as the subjective desire to drink and urge as the behavioral intention or impulse to drink, while Robinson and Berridge (1993) define craving as intensely wanting drugs. According to the Elaborated Intrusion theory of desire (Kavanagh, Andrade, & May, 2005), craving is an intense desire or urge, with desire being a cognitive and affective event with frequency and duration, and is distinguishable from physiological withdrawal symptoms.

In this thesis, we define craving as an acute increase in the urge to drink alcohol, a phenomenon that continuously varies in intensity, frequency and duration.

Craving plays an important causal role in various models of relapse (Franken, 2003; Garland, Boettiger, Gaylord, Chanon, & Howard, 2011). For example, the Incentive Sensitization theory (Robinson & Berridge, 1993) claims that incentive salience is attributed to stimuli that have been accompanied by repeated alcohol use in the past. As a result, the individual becomes sensitized to the incentive salience of the stimuli and 'wanting' alcohol is transformed into excessive craving. Craving, in turn, can initiate addictive behavior such as compulsive alcohol seeking and alcohol consumption. However, the results of studies investigating the causal role of craving in relapse remain inconclusive (Drummond, 2001). For example, Holt et al. (2012) found that craving did not predict relapse in alcohol-dependent patients undergoing treatment. In contrast, other studies found that craving does predict relapse in alcohol-dependent patients (Higley et al., 2011; Miller et al., 1996).

Determinants of craving

As discussed, the role of craving in predicting relapse is still under debate. Despite the inconclusive results, craving is a widely studied concept in addiction because it can be very intrusive and interfere with daily life in abstinent alcohol-dependent patients (Tiffany & Wray, 2012). This thesis makes a clear distinction between determinants of craving and determinants of relapse since there is still debate on the role of craving in relapse while the determinants of relapse and craving do show similarities. Clinical studies

have demonstrated that most alcohol-dependent patients do not typically experience intense craving (Glöckner-Rist, Lémenager, & Mann, 2013; Oslin, Cary, Slaymaker, Colleran, & Blow, 2009; Tiffany, 1990). In addition, craving does not always produce or precede a relapse (Drummond, 2001; Higley et al., 2011; Miller et al., 1996). The determinants of craving under investigation in this thesis will be discussed below.

Negative affect

As with relapse, craving is often provoked by negative affect. Cue reactivity research has shown that in alcohol-dependent patients, craving is often provoked in response to a negative affect induction. Several laboratory studies have shown that stress, as a type of negative affect, can provoke craving in alcohol-dependent patients (Fox, Bergquist, Hong, & Sinha, 2007; Sinha et al., 2009).

Alcohol-related stimuli

As with negative affect, craving in response to alcohol-related stimuli has been widely studied in the laboratory. Results from these studies have consistently shown that alcohol-related stimuli provoke craving in alcohol-dependent patients (Carter & Tiffany, 1999; Fox et al., 2007; Sinha et al., 2009).

Drinking motives

Many alcohol-dependent patients report that, before treatment, they consumed alcohol to relieve negative affect (Kushner et al., 2001), which is also known as drinking to cope with negative affect (i.e., coping motives; Cooper, 1994). When maintaining abstinence, drinking to cope with negative affect is not possible if an individual experiences negative affect, and as a consequence feelings of craving may emerge (e.g., Tiffany, 1990). For example, social drinkers with high levels of coping motives show greater increases in alcohol craving after a stressful mood induction than those with low levels of coping motives (Field & Powell, 2007; Field & Quigley, 2009). Since there is not much known about the role of coping motives in evoking craving in abstinent alcohol-dependent patients, we investigate the role of these coping motives in relation to craving in this thesis.

Research questions

As stated before, the overall aim of this thesis is to explore proximal determinants of relapse and craving in abstinent alcohol-dependent

outpatients. To fulfill this aim, five research questions will be answered in the following chapters of this thesis. First, what do alcohol-dependent patients themselves report as being determinants of relapse and of craving? Second, is sensitivity for alcohol-related cues enhanced by stress? Third, are attentional bias and approach/avoidance tendencies predictors of relapse in alcohol-dependent outpatients? Fourth, are trait anxiety and drinking motives related to craving? And finally, do stress, negative affect and abstinence motivation change when patients experience temptation episodes? Table 1 displays an overview of the chapters in this thesis and their accompanying research questions.

Table 1. *Overview of research questions and accompanying chapters*

Research question	Chapter
What do alcohol-dependent patients themselves report as being determinants of relapse and of craving?	2
Is sensitivity for alcohol-related cues enhanced by stress?	3
Are attentional bias and approach/avoidance tendencies predictors of relapse in alcohol-dependent outpatients?	4
Are trait anxiety and drinking motives related to craving?	5
Do stress, negative affect and abstinence motivation change when patients experience temptation episodes?	6
General discussion	7

Thesis overview

Following this introductory chapter, chapters 2 through 6 present five empirical studies. The second chapter of this thesis explores the self-reported determinants of relapse and craving in alcohol-dependent patients using semi-structured interviews. Chapter three provides an overview of available literature on the relationship between stress and sensitivity for

alcohol-related cues. The fourth chapter investigates whether attentional bias and approach/avoidance tendencies are predictive of relapse by measuring attentional bias and approach/avoidance tendencies in alcohol-dependent patients at the start of treatment and following up on relapses within three months after measuring these implicit processes. Additionally, we examine if time to relapse is a more sensitive outcome measure for relapse than a binary relapse variable. Chapter five investigates the relationship between anxiety and craving and the influence of coping motives on this relationship by assessing trait anxiety, drinking motives, and craving during treatment in alcohol-dependent patients at the beginning of outpatient treatment. Additionally, the relationship between craving and pretreatment alcohol consumption is also investigated. In chapter 6, Ecological Momentary Assessment methodology (EMA; for an explanation, see Box 1) is used to map the natural history of temptation episodes in alcohol-dependent outpatients, and compares the intensity of these temptation episodes between patients who relapsed during the study and those who did not relapse. The general discussion in the seventh and final chapter combines results, presents limitations and overall conclusions, and provides directions for future research.

Box 1. Description of EMA methodology

EMA methodology

Ecological Momentary Assessment is a methodology for investigating behaviors in naturalistic settings, which has also been proven useful in studies on substance use (Shiffman, 2009). Ecological momentary assessment (EMA) is particularly suitable for studying substance use, because use is episodic and thought to be related to mood and context. This article reviews EMA methods in substance use research, focusing on tobacco and alcohol use and relapse, where EMA has been most applied. Common EMA designs combine event-based reports of substance use with time-based assessments. Approaches to data organization and analysis have been very diverse, particularly regarding their treatment of time (Marhe et al., 2013; Shiffman & Waters, 2004).

Compliance with signaled assessments is often high. Compliance with recording of substance use appears good but is harder to validate. Treatment applications of EMA are emerging. EMA captures substance use patterns not measured by questionnaires or retrospective data and holds promise for substance use research.

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Chapter 2: Relapse and Craving in Alcohol-Dependent Individuals: a Comparison of Self-Reported Determinants

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Abstract

Background: Negative affective states and alcohol-related stimuli increase risk of relapse in alcohol dependence. In research and in clinical practice, craving is often used as another important indicator of relapse, but this lacks a firm empirical foundation.

Objectives: The goal of the present study is to explore and compare determinants for relapse and craving, using Marlatt's (1996) taxonomy of high risk situations as a template.

Methods: We conducted semi-structured interviews with 20 alcohol-dependent patients about their most recent relapse and craving episodes. Interview transcripts were carefully reviewed for their thematic content, and codes capturing the thematic content were formulated.

Results: In total, we formulated 42 relapse-related codes and 33 craving-related codes. Descriptions of craving episodes revealed that these episodes vary in frequency and intensity. The presence of alcohol-related stimuli ($n = 11$) and experiencing a negative emotional state ($n = 11$) were often occurring determinants of craving episodes. Both negative emotional states ($n = 17$) and testing personal control ($n = 11$) were viewed as important determinants of relapses. Craving was seldom mentioned as a determinant for relapse. Additionally, participants reported multiple determinants preceding a relapse, whereas craving episodes were preceded by only one determinant.

Conclusions: Patient reports do not support the claim that craving by itself is an important proximal determinant for relapse. In addition, multiple determinants were present before a relapse. Therefore, future research should focus on a complexity of different determinants.

Introduction

Despite years of research, levels of relapse in individuals with alcohol dependence remain high, and 45-75% of patients relapse within one year after treatment (Boothby & Doering, 2005). Several theories and models have been developed to explain why relapse occurs, and craving is an important causal factor in many of these models (Franken, 2003; Garland, Boettiger, Gaylord, et al., 2011). The Incentive Sensitization Theory (Robinson & Berridge, 1993), which adopts a neurocognitive perspective to relapse, claims that incentive salience is attributed to stimuli that have been accompanied by repeated alcohol use in the past. As a result, the individual becomes sensitized to the incentive salience of the stimuli and wanting drugs or alcohol is transformed into excessive craving. Craving, in turn, can initiate addictive behavior such as compulsive drug/alcohol seeking and drug/alcohol taking.

Witkiewitz and Marlatt (2004) present a broader, dynamic model of relapse. According to this model, various factors elevate the risk of relapse in high-risk situations, and relapse is due to the interaction between determinants. Relapse determinants fall into five categories: affective states; coping skills; physical withdrawal states; cognitive processes such as craving and motivation; and background factors such as family history, and years of dependence. The authors distinguish between tonic processes and phasic responses. Tonic processes, which determine the individual's chronic vulnerability to relapse, include background factors, cognitive processes and physical withdrawal states. These processes often accumulate and provide the foundation for relapse. In the dynamic model, the phasic response is the critical point at which behavioral responding due to affective state or coping behaviors influences substance-using behavior.

Thus, whereas Incentive Sensitization Theory emphasizes craving, the dynamic model of relapse only regards craving as one of many possible determinants in the phasic response of relapse. Nevertheless, the phenomenon of craving is one of the most researched concepts in addiction (Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005; Franken, 2003; Tiffany & Wray, 2012). The goal of the present study is to explore the determinants for relapse and craving, and the role of craving in relapse.

One issue with the concept of craving is the lack of a clear consensus regarding its definition (Kozlowski & Wilkinson, 1987). Marlatt and Donovan (2005) define craving as the subjective desire to drink and urge as the behavioral intention or impulse to drink. In contrast, Robinson

and Berridge (1993) define craving as intensely wanting drugs. In the present study, we adopted a broad definition of craving: a phenomenon that continuously varies in intensity, frequency and duration (Kavanagh et al., 2013, 2005).

Clinical studies have demonstrated that most alcohol-dependent patients do not typically experience intense craving (Glöckner-Rist et al., 2013; Oslin et al., 2009). In addition, craving does not always precede or produce a relapse (Drummond, 2001). Even though the results of studies on craving as a determinant of drinking and/or relapse are inconclusive, still many neurocognitive studies include some measure of craving. For example, Holt et al. (2012) found that craving did not predict subsequent relapse in alcohol-dependent patients undergoing treatment. In contrast, other studies have found that craving predicts relapse in alcohol-dependent patients (Higley et al., 2011; Miller et al., 1996). Two explanations (which are not mutually exclusive) are possible. Craving may be absent when a relapse occurs, and craving may occur without instigating a relapse. We believe that for research purposes, it is important to know whether craving is a reliable proxy for relapse. For clinical purposes, this determines the need to worry about cravings that do not instigate a relapse.

An attempt to categorize self-reported determinants of a relapse was made by Marlatt (1996). He developed a taxonomy of high risk situations for relapse into substance use. Marlatt's taxonomy distinguishes between intrapersonal and interpersonal determinants. Intrapersonal determinants are related to the individual or their reactions to environmental events, such as negative and positive emotional states or testing personal control. Interpersonal determinants involve the presence or influence of others that precipitate the relapse in the preceding 24 hours. Examples of interpersonal determinants include interpersonal conflict, and social pressure (Marlatt, 1996; Marlatt, Stout, & Zywiak, 1996). This taxonomy has been tested among alcoholics, smokers and other addicts by Marlatt (1996), and others have used it to categorize relapse determinants, both in smokers (Piñeiro & Becoña, 2013) and in depressed alcohol-dependent men (Strowig, 2000). However, to our knowledge there are no studies that have characterized determinants of craving using Marlatt's taxonomy (1996). Doing this can offer insight in the role of craving as a determinant for relapse.

In the current study, we first identify self-reported determinants of both relapse and craving in a sample of alcohol-dependent patients. Based

on that, we explore the determinants participants report as being precursors of their relapse and their craving episodes. Additionally, we determine which determinants are mentioned most often, and the extent to which craving is a determinant of relapse in alcohol-dependent individuals. Second, we investigate differences in situations in which craving triggers a relapse and those in which craving does not trigger a relapse. The present study might thereby provide an explanation for findings that craving does not invariably precede a relapse.

Method

Participants

Twenty patients were recruited from five different addiction treatment centers in the Netherlands using a criterion sampling strategy. At the time of the interview, seven patients followed an aftercare program and 13 patients were in outpatient treatment. The seven participants in aftercare completed a 20-day inpatient program based on the Minnesota Model before entering aftercare. The 13 patients participating in an outpatient program received treatment that combined cognitive behavioral therapy with motivational interviewing techniques.

All participants met the following inclusion criteria: (a) primary diagnosis of alcohol dependence, (b) a relapse to pretreatment drinking levels, (c) literacy in Dutch at the primary school level, and (d) a minimum age of 18 years. Exclusion criteria were: (a) the presence of an Axis II disorder, (b) the presence of a psychotic disorder, or (c) dependence on substances besides alcohol and nicotine. Eligibility was assessed by therapists at the participating treatment centers when a patient reported that he or she had relapsed, and reviewed by the interviewer (MS). Eligible patients were then asked to participate in the study. None of the research team members were involved in the participants' treatment and participants were told that their responses would not influence their treatment.

All participants provided informed consent before the start of the interview and received € 10 compensation for participation. The Medical Ethical Committee of the Erasmus Medical Centre indicated that the committee had no objections to the execution of this research.

Procedure

Demographic data (e.g. age, gender, education level) were obtained at the beginning of the interview. The functional analysis of relapse, a component of the Community Reinforcement Approach (Azrin, 1976), and Marlatt's (1996) taxonomy of high-risk situations served as sensitizing concept when formulating the interview questions. The interview questions focused on the following topics: patients' drinking history, treatment history, craving episodes and the most recent relapse. The topics of craving and relapse included questions concerning the patient's definition of craving and relapse, the frequency and intensity of cravings, and self-reported determinants of craving and relapse such as feelings, thoughts, or surroundings, and whether the participant had experienced craving prior to the relapse. In the interviews, we only discussed the participants' most recent relapse into pretreatment drinking levels. Moreover, we also focused on the craving episode itself without distinguishing between craving, urge and desire.

A psychotherapist who had experience working with the target population of the study reviewed the questions. Based on her feedback, questions were simplified to make them clearer and more understandable to participants. After the first four interviews, the questions were reviewed to determine the extent to which they captured the information that we wished to obtain from the participants. Minor adjustments in wording were made, but no questions were added or removed. No new information emerged after having conducted a total of 16 interviews. At that point we decided that we would stop interviewing after a total of 20 interviews under the condition that no new information would emerge during these final four interviews.

All 20 interviews were administered by the same researcher (MS) and were audiotaped. Interviews lasted from 30 to 50 minutes and were transcribed verbatim. Another member of the research team (TS) reviewed all of the transcripts to provide feedback on the interview content and process and to determine the extent to which topics or questions should be modified. No questions were modified, added or removed during the review process.

Data analysis

After transcription, the interviews were independently coded by two researchers (MS, JE) under the supervision of a third researcher (TS), using QualiCoder, a web-based analyzing program ("Qualicoder," 2013). The first round of coding consisted of open coding, which involved reading the

transcripts sentence by sentence and using in vivo codes (i.e., specific codes derived from the participants' terminology) to capture relevant information. The coding of the two researchers was then compared with each other to identify overlap and discrepancies in coding. After in-depth discussion, the codebook was finalized, containing 42 unique codes related to relapse determinants and 33 codes related to craving determinants. The final codebook was then used to recode all of the interviews, and inter-rater reliability was calculated. Two researchers independently coded two randomly chosen interviews using the final coding scheme. The initial inter-rater agreement was 72.6%. Discrepancies were carefully reviewed and resolved, and the results of the review process were integrated in the coding of all interviews. The aforementioned steps were all carried out using QualCoder (2013).

After reviewing the codebook we investigated how we could compare the determinants of craving and relapse. The reported determinants of both relapse and craving showed many similarities with the categories of the taxonomy of high risk situations developed by Marlatt (1996). We decided to use this taxonomy as a template for comparing the determinants of relapse and craving since all determinants fit the framework (see Tables 1 and 2).

Table 1. *Marlatt's Taxonomy Applied to Relapse Determinants*

I.	Intrapersonal-environmental determinants
A.	Coping with negative emotional states (<i>n</i> = 17)
i.	Coping with frustration and/or anger <i>Frustration prior to relapse</i> <i>Relapse due to frustration and dissatisfaction with work</i>
ii.	Coping with depression <i>Unhappy prior to relapse</i> <i>Feeling sad prior to relapse</i> <i>Relapse due to loss of contact with one's son</i> <i>Relapse due to a divorce</i>
iii.	Coping with anxiety <i>Feeling anxious prior to relapse</i>
iv.	Coping with other negative emotional states <i>Being emotional prior to relapse</i> <i>Feeling helpless prior to relapse</i> <i>Feeling not so well prior to relapse</i> <i>Feeling bad prior to relapse</i> <i>Feeling lonely prior to relapse</i> <i>Hopeless situation of unemployment prior to relapse</i> <i>Disappointment about theft of one's stepson prior to relapse</i> <i>Not talking about feelings prior to relapse</i> <i>Stress prior to relapse</i> <i>Leaving one's former residence prior to relapse</i>
B.	Coping with negative physical-physiological states (<i>n</i> = 2)
i.	Coping with physical states related to prior substance use -
ii.	Coping with other negative physical states <i>Being tired prior to relapse</i> <i>Having trouble sleeping prior to relapse</i>
C.	Enhancement of positive emotional states (<i>n</i> = 3)
	<i>Feeling cheerful prior to relapse</i> <i>Feeling sociable prior to relapse</i> <i>Being fed up with everything prior to relapse</i>
D.	Testing personal control (<i>n</i> = 7)
	<i>Consciously starting to drink</i> <i>Consciously giving in to an impulse to drink</i> <i>Drinking the first glass</i> <i>Allowed to drink again</i> <i>Wanting to engage in controlled drinking</i> <i>Drinking leftovers</i> <i>'Your brains tell you to drink'</i>

E.	Giving in to temptation or urges (<i>n</i> = 6)
i.	In the presence of substance cues <i>Presence of good quality wine</i> <i>Desire to drink prior to relapse</i> <i>Relapse in a restaurant</i>
ii.	In the absence of substance cues <i>Craving (trek) prior to relapse</i> <i>Not being able to withstand drinking prior to relapse</i> <i>Tunnel vision prior to relapse</i>
II.	Interpersonal determinants
A.	Coping with interpersonal conflict (<i>n</i> = 4)
i.	Coping with frustration and/or anger <i>Conflict with spouse prior to relapse</i> <i>Frustration over loss of job</i>
ii.	Coping with depression -
iii.	Coping with anxiety -
iv.	Coping with other negative emotional states <i>Disappointed in one's stepson prior to relapse</i> <i>Losing a job prior to relapse</i>
B.	Social pressure (<i>n</i> = 2)
i.	Direct social pressure <i>Friends visiting prior to relapse</i> <i>Presence of alcohol</i>
ii.	Indirect social pressure -
C.	Enhancement of positive emotional states (<i>n</i> = 1) <i>Relapse at a party/social gathering</i>

Note: (*n* = ...) represents the number of codes for each main category

The codes from the final codebook were categorized using Marlatt's (1996) taxonomy. We distinguished between codes related to relapse and codes related to craving, following the indexing rules provided by Marlatt and colleagues (1996) in classifying each code into one of the taxonomy categories. However, we were not as strict as Marlatt and colleagues in only selecting the determinants that were reported as the main reason for relapsing. We included all determinants reported by the participants in order not to miss any valuable information.

To classify codes involving craving into the categories in Marlatt's taxonomy, the labeling of categories and subcategories was modified to reflect the craving situation (see Table 2).

Table 2. *Marlatt's Taxonomy Applied to Craving Determinants*

I.	Intrapersonal-environmental determinants
A.	Confronted with/presence of negative emotional states ($n = 11$)
i.	frustration and/or anger <i>craving due to frustration</i>
ii.	Confronted with/presence of depression <i>craving due to depressive feelings</i> <i>desire due to sadness</i>
iii.	Confronted with/presence of anxiety <i>craving due to nervousness</i> <i>craving due to agitation</i> <i>craving due to fear of the unknown</i>
iv.	Confronted with/presence of other negative emotional states <i>chance of experiencing craving increases when in a negative mood</i> <i>craving due to dissatisfaction with self</i> <i>craving due to feeling bad</i> <i>craving due to feeling lonely</i> <i>craving due to feeling pitiful</i>
B.	Confronted with/presence of negative physical-physiological states ($n = 2$)
i.	Confronted with/presence of physical states related to prior substance use -
ii.	Confronted with/presence of other negative physical states <i>Being tired prior to relapse</i> <i>Having trouble sleeping prior to relapse</i>
C.	Confronted with/presence of positive emotional states ($n = 3$) <i>Craving is a thought of a pleasurable moment</i> <i>Craving when feeling sociable</i> <i>Craving when you want to celebrate something</i>

-
- D. Testing personal control ($n = 1$)
 - Craving after drinking the first glass*
 - E. Craving in the presence of external substance cues ($n = 11$)
 - Craving due to thinking of drinking*
 - Craving when seeing a pub*
 - Craving when seeing a liquor store*
 - No strong craving, but light craving when in a pub*
 - Bottle of wine is a trigger for craving*
 - Craving when hearing music from the eighties*
 - Craving when seeing alcohol in the grocery store*
 - Craving when seeing advertisements for alcohol*
 - Craving due to nice weather*
 - Craving after working in warm weather*
 - Craving is stronger when engaging in controlled drinking*
- II. Interpersonal determinants
- A. Confronted with/presence of interpersonal conflict ($n = 3$)
 - i. Confronted with/presence of frustration and/or anger
 - Craving due to arguments*
 - Craving due to confrontation with one's father*
 - ii. Confronted with/presence of depression
 -
 - iii. Confronted with/presence of anxiety
 -
 - iv. Confronted with/presence of other negative emotional states
 - Craving due to suffering injustice*
 - B. Social pressure ($n = 2$)
 - i. Direct social pressure
 -
 - ii. Indirect social pressure
 - Craving due to seeing others drink*
 - Craving when I'm sitting at a sidewalk cafe with my partner who is drinking a glass of wine*
 - C. Confronted with/presence of positive emotional states ($n = 0$)
-
- Note: ($n = \dots$) represents the number of codes for each main category*

Category labels for the craving taxonomy that included the phrase ‘coping with ...’ (e.g., coping with anxiety) were changed into ‘confronted with ...’ (e.g., confronted with anxiety) because this phrase was more appropriate for craving (i.e., craving is not a way to cope with anxiety, but can occur when one is anxious). Additionally, we changed the IE category of ‘giving in to temptation or urges, in the presence [IEi] or absence [IEii] of substance cues’ to ‘craving in the presence of external substance cues’. This category included the codes related to craving that mentioned an external cue that triggered a craving episode. Because all craving episodes triggered by internal cues (e.g., affective states) were categorized using categories IA through ID, we did not separate the IE category into two subcategories, but did retain the subcategories in the relapse taxonomy.

Results

Sample characteristics

The sample consisted of 20 alcohol-dependent patients currently in treatment who had recently relapsed. Sample characteristics are displayed in Table 3.

Table 3. *Sample characteristics.*

	Overall (n = 20)	
	M	SD
Age	48	12
Proportion men (in %)	75	-
Educational level (in %)		
Vocational education	25	-
Higher vocational education	20	-
University	45	-
Other	10	-
Employment status (in %)		
Employed	25	-
unemployed	75	-
Treatment goal (in %)		
Abstinence	80	
Controlled drinking	20	

Personal definitions of relapse

We asked our participants what their personal definition of a relapse is. Participants could be categorized into two groups based on their definitions of relapse. The first group (n=7) viewed relapse as returning to the pretreatment drinking levels, as one of our participants stated: “A relapse is really starting to drink eight cans of beer overnight. Drinking really heavily”. Three participants of this group were currently abstinent, the remaining four were controlled drinkers.

The second group (n=13) considered drinking any amount of alcohol as a relapse. This second definition is seen mostly in participants whose current treatment goal was abstinence and is illustrated by the following: “Relapsing is when you are not doing what you intended to do, and that is never to drink again.”

Personal definitions of craving

Currently there is no scientific or clinical consensus regarding the definition of craving. Therefore, we asked participants to describe their own understanding of craving. The definitions of craving provided by the participants were diverse but the definitions did share a common phenomenon: craving involves a need for alcohol. For example, one participant stated: "I think craving for me is the association of alcohol with sociability. But that's the case with almost everything, there's always a reason why a drink should accompany any moment."

Another participant viewed craving as "a devil on my shoulder". She stated: "On one shoulder, there is that little devil. The little angel is sitting on my other shoulder. Craving is when the devil gets stronger than the angel."

The intensity of craving and frequency of episodes varied between and within participants, but the need for alcohol was always present. Reported frequencies of craving episodes ranged from once every three to four months to daily episodes.. For example, one of the participants, who used to experience strong feelings of craving, stated: "Before my treatment, I had very strong cravings. You're thinking, oh dear, I need to take a glass of wine, I really want it right now."

In contrast, some participants reported experiencing little to no intense craving: "I could be standing in the grocery store, looking at cans of Bacardi and Coke. Then, I think, that would be nice. I don't have that a lot, but it pops up sometimes."

Some participants experienced different types of craving, as the following participant stated:

Craving is the beginning of desire. Craving is like the thought of a pleasurable moment. Desire is a feeling or an urge that is harder to ignore. (...) Craving is when you have brief thoughts while you're trying really hard not to drink. (...) Then you replace these thoughts and that is not something you cannot resist. What you're afraid of is that desire.

We included all types of craving episodes in our analyses.

Some participants experienced craving as less intrusive and transient, while others had to exert considerable effort to resist their craving, for example:

I was traveling by train, and I just craved a cigarette with a drink and a cup of coffee. I was thinking, what should I do?! Should I get out,

but I thought if I'd do that, I would never reach my destination. (...) I didn't do it, but it was really hard.

Taxonomy of relapse determinants

All 42 determinants that were related to relapse could be categorized using Marlatt 's (1996) taxonomy of high-risk situations. For the relapse taxonomy, 83.4% of the determinants were categorized as intrapersonal, and 16.6% were categorized as interpersonal determinants (see Table 4).

Table 4. *Frequencies of determinants in Percentages per Category*

Situation	Relapse codes (<i>n</i> = 42)	Craving and temptation codes (<i>n</i> = 33)
I. Intrapersonal determinants	83.4	84.8
IA. Negative emotional states	40.5	33.3
IB. Negative physical states	4.8	6.1
IC. Positive emotional states	7.1	9.1
ID. Testing personal control	16.7	3.0
IE. Urges and temptations (presence of external cues)	14.3	33.3
II. Interpersonal determinants	16.6	15.2
IIA. Interpersonal conflict	9.5	9.1
IIB. Social pressure	4.8	6.1
IIC. Positive emotional states	2.4	-

Most determinants involved negative emotional states, such as feeling bad, sad or anxious prior to the relapse. As one participant stated: "At one point I thought, well, if I just take a drink, I'll lose that bad feeling for a while". Another category of determinants which was quite large, regarded testing of personal control over drinking alcohol. Participants would start to drink in a controlled manner, because they believed they would be able to control themselves and just drink moderately, but often this was not possible, as this participant said:

So I went from being sober to consciously starting to drink. There was no reason, just trying it because I enjoy it, and I believe it

[alcohol] fits with certain things. Just seeing how things would go.
But that really didn't work.

Craving did not appear to be an important determinant, since craving was present before the relapse in only four of the twenty cases. Those participants who reported the presence of craving before their relapse indicated that craving was present in the hours before the relapse. Also, only a small proportion of the determinants could be categorized under the category 'giving in to temptation or urges'. Craving could occur in both in presence of alcohol stimuli or without these stimuli. As one participant stated: "And then suddenly, I just craved a pack of wine (...). And the next day, I saw that empty pack of wine on the kitchen counter."

We did not find any determinants that would fit the taxonomy's IBI subcategory of 'coping with physical states related to prior substance use'; the absence of any withdrawal-related determinant could be explained by the fact that all our participants were abstinent for at least 14 days before they relapsed.

Taxonomy of craving determinants

We were able to categorize all 33 determinants of craving using the taxonomy. Table 2 presents an overview of the taxonomy and the modified category labels. For craving, 84.8% of the determinants were intrapersonal, whereas the remaining 15.2% of the determinants were interpersonal. The percentages for the categories IA through IIC are displayed in Table 4. The two largest categories were 'negative emotional states' and 'craving in presence of external substance cues'. Each category contained one third of all craving determinants. As an example of a negative emotional state as determinant of craving, one of the participants stated: "Last week I was really feeling down, everything was such a drama and then I thought, I could drink one two drinks right now". Examples of external substance cues were very diverse and included grocery stores, alcohol commercials, nice weather, seeing a bottle of wine, and watching someone else drink alcohol. Again, we found no determinants that could be categorized under 'confronted with negative physical-physiological states'. There were also no reports of craving episodes without a clear determinant.

Comparison of the relapse and craving taxonomies

Comparison of the relapse and craving taxonomies revealed a comparable distribution of determinants across the two primary categories (intrapersonal

and interpersonal). The intrapersonal category contained 83.3% of total number of relapse determinants and 84.9% of the craving determinants.

Within the intrapersonal category, most relapse determinants were classified into the categories 'coping with negative emotional states' (IA) and 'testing personal control' (ID), while most craving determinants were classified into 'coping with negative emotional states' (IA) and 'temptation or urges in the presence of external cues' (IE). The IA category (i.e., negative states) for both relapse and craving included determinants such as 'feeling bad prior to relapse/craving due to feeling bad' and 'stress prior to relapse/craving due to stress'.

There was a difference between craving and relapse in the ID category (i.e., testing control). For relapse, testing personal control indicated that an individual wanted to drink in a controlled manner but could not maintain control and relapsed. For craving, testing personal control indicated that the individual was drinking in a controlled manner, and the controlled drinking triggered craving.

The main difference between the relapse determinants and the craving determinants was related to the IE category (i.e., 'temptation and cues'). For relapse, all determinants that contained craving were assigned to this category. For craving, we assigned determinants that contained external cues for craving to this category; for example, seeing alcohol in the grocery store or viewing an advertisement for alcohol. In the craving taxonomy, the IE category was one of the two largest categories, with one third of the cravings triggered by external alcohol-related cues. In contrast, fewer cases (14.3%) were classified in the IE category in the relapse taxonomy. These findings indicated that craving was not a necessary or an important determinant of relapse.

Comparison of relapse and craving at the case level

Another difference between relapse and craving was found when reviewing the individual interviews. All but one participant reported that a single determinant precipitated a craving episode, whereas all participants reported that two or more determinants triggered relapses. These results indicate that multiple determinants were required to produce a relapse, while a single determinant was sufficient to initiate a craving episode.

The number of determinants preceding a relapse ranged from two to six. One of the participants explicitly stated that her relapse was due to the accumulation of determinants: "Often it is, well, of course, it is a combination

of factors. It never happens that you receive a phone call and then you relapse. It doesn't work that way. It is an accumulation."

Discussion

In the present study, we explored self-reported proximal determinants of relapse and craving in a sample of alcohol-dependent patients. We used Marlatt's (1996) taxonomy of high risk situations as a template to compare relapse and craving determinants. The craving determinants fit the taxonomy well, and the determinants for relapse and craving exhibited similar distributions overall across the taxonomy. Even though the taxonomy has been used in multiple studies (Marlatt, 1996; Piñeiro & Becoña, 2013; Strowig, 2000) there are signs that the reliability of the taxonomy is inconsistent for comparing results based on the taxonomy across independent studies (Longabaugh, Rubin, Stout, Zywiak, & Lowman, 1996). Therefore, generalizability of our results to other samples is difficult. However, the goal of the current study was exploratory and we sought to find self-reported determinants of craving and relapse, which in hindsight fit the taxonomy well.

The study findings indicate that patients in our sample did not consider craving by itself to be an important determinant of relapse. It was infrequently reported as a relapse determinant and was never the sole determinant of relapse, which was always associated with more than one determinant. It should be noted however, that the interviews and analyses focused on risk factors influencing relapse and craving. Further studies may need to incorporate protective factors as well. For example, it may be that in cases where craving was present without relapse, competing desires had prevented individuals from drinking (cf. Ambivalence Model of Craving; Breiner et al., 1999; Stritzke et al 2007) by motivating them to exert inhibitory control over their desire to drink.

The results also indicate that negative emotional states are an important determinant of both relapse and craving. Differences between craving and relapse were primarily found for the determinant 'substance-related cues': Craving was triggered by external substance cues in a third of the cases, whereas relapse was triggered by substance cues in a mere 14 percent of the cases.

The finding that negative emotional states are important determinants of both relapse and craving is consistent with Baker and colleagues' (2004) Affective Processing Model of Negative Reinforcement.

This model proposes that the accumulation of negative affect due to the presence of stressors elicits renewed substance use. Also, the relapse determinants resembled the phasic responses (i.e., negative emotional states) described in Witkiewitz and Marlatt's (2004) dynamic model of relapse, which is supported by the finding that multiple determinants always preceded relapses.

One limitation to the study is that due to the nature of the study, the sample size was small and heterogeneous. Therefore, it is not possible to draw firm quantitative conclusions from the study data. Further research with larger samples is required to confirm the study findings regarding the factors that trigger craving episodes and relapse. This is especially the case for craving, since to our knowledge, the present study is the first to use Marlatt's taxonomy to categorize self-reported determinants of craving.

Because the study relies upon self-report, recollection bias might have influenced study results. As a result, it is possible that the reports of craving episodes were biased because these episodes may have been less salient to participants. Memories of craving episodes might be less vivid than memories of relapse episodes because relapse episodes have a greater impact on the individual. Despite the use of self-report, the present study provides a rather comprehensive picture of the patient's perception of relapse, craving, and relapse and craving triggers. In addition, our results are in line with experimental studies showing that craving was not a proximal predictor of relapse (Cooney et al., 2007; Holt et al., 2012), making it less likely that recall bias affected the recollection of our participants regarding the presence of craving prior to a relapse.

The study is clinically relevant, since it suggests that the immediate risk of relapse from momentary or acute cravings is not necessarily high. The relationship has also been studied in research using Ecological Momentary Assessment (EMA) methodology (Shiffman, 2009). In these studies, participants' craving (and other variables) is monitored in daily life using electronic devices. Participants are prompted to fill out questions at random times throughout the day. Studies using EMA did show associations between craving and relapse in non-abstaining alcohol-dependent individuals (Fazzino, Harder, Rose, & Helzer, 2013; Kavanagh, May, & Andrade, 2009). However, in abstaining alcohol dependent patients, an association has only been found in subgroups of patients: in patients with relatively severe dependence and mood disturbance (Litt, Cooney, & Morse, 2000), and in patients with relatively high alcohol craving states that do not

change during the initial period of abstinence (Oslin et al., 2009). Taken together, when looking at the results of the current study and existing research on craving as a predictor of relapse, a strong focus on craving during treatment seems not always warranted.

However, craving continues to be valuable as a distal predictor, particularly in the diagnosis of alcohol dependence and the prediction of drinking behavior or relapse in the more distant future (Casey, Adamson, Shevlin, & McKinney, 2012; Connolly et al., 2013). Treatment should continue to address ways to deal with craving due to the potential future effects of craving on relapse. Because examining these distal effects was beyond the scope of the present study, future research should investigate the exact nature of these more long-range effects. Furthermore, future research on these topics should not be limited to the laboratory, but should investigate the extent to which determinants of these phenomena operate and interact in daily life. One way to accomplish this is to measure all possible proximal predictors of relapse and of craving using EMA methodology to examine under which circumstances craving indeed predicts a relapse. In our opinion, it is essential that future research use EMA to measure craving and relapse as well as craving and relapse determinants.

In summary, we found that patients did not consider craving by itself to be an important proximal determinant for relapse. Research thus should not use self-reports of craving as a proximal determinant of relapse unless relapse is also measured. Our results further indicate that relapse depends upon multiple determinants, whereas craving can be triggered by a single determinant. This suggests that craving in itself, or a single determinant of craving, does not constitute a major risk for relapse unless it coincides with other proximal risk factors.

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Chapter 3: The relationship between perceived stress and cue sensitivity for alcohol.

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Abstract

Previous research has shown that cue sensitivity and stress affect the risk for relapse in alcohol-dependent patients. Theoretically, a link between the two can be expected. However, a clear overview of the interplay of these factors is not yet available. The purpose of this review was to examine the empirical evidence for the influence of stress on sensitivity for alcohol-related cues.

Empirical studies indexed in PubMed, EMBASE, PsycINFO, and Web of Knowledge that assessed the relation between stress and sensitivity for alcohol-related cues using subjective, behavioral and/or physiological measures were included in the review.

Of the 359 articles screened, 12 were included in the review. Nine articles supported the existence of the relationship between stress and heightened cue sensitivity for alcohol-related cues, whereas three articles did not support our hypothesis.

We conclude that the relationship between stress and sensitivity to alcohol cues appears to exist. In fact, there may be different factors at play: our review points toward (1) differences between the effect of psychological stress and physiological stress on cue-sensitivity, and (2) individual differences regarding coping drinking which may explain stress-induced cues sensitivity.

Introduction

Despite years of research and great progress in developing treatments for alcohol dependence, rates of alcohol relapse remain high (Boothby & Doering, 2005; Finney et al., 1996). A number of theories regarding the reasons for relapse focus on the role of stress and sensitivity for alcohol-related cues or 'stimuli.' For example, according to the Affective Processing Model of Negative Reinforcement (Baker et al., 2004), stressors cause or increase negative affect, which in turn activates the learned rewarding properties of alcohol (or other addictive substances) that relieve negative affect, thereby motivating the individual to use again.

Another factor contributing to increased risks of relapse is cue sensitivity. Hereby we mean that the brain is sensitive to alcohol-related cues, leading to a strong reaction toward these cues, i.e., cue reactivity. According to the Incentive Sensitization Theory (Robinson & Berridge, 1993), specific cues (e.g., stimuli, situations) become associated with an addictive substance through repetitive use in the presence of these cues. The substance-related cues become attractive and therefore salient to the addict and activate a neurological hypersensitive reaction to a substance (Grüsser et al., 2004; Tapert et al., 2003). This hypersensitivity may remain even after long periods of abstinence (Robinson & Berridge, 2001, cf. Koob & Le Moal, 2001).

Combining the two aforementioned theories, we hypothesized that under stress, cues that have become associated with alcohol via previous experience become more salient, and the brain is more sensitive to these cues.

In experimental studies, stress has been induced by various types of stressors. Dickerson and Kemeny (2004) categorized acute psychological stressors into five types of stress induction procedures: performance of cognitive tasks; public speaking with verbal interaction; a combination of the aforementioned; noise exposure; and real (e.g., pictures, film) or mental (i.e., imagination, recall) exposure to emotion-eliciting material or situations. All five types of stress induction evoke psychological distress, and public speaking combined with a cognitive task also evokes physiological stress.

There are a number of methods to assess cue sensitivity: physiological measures, subjective measures, behavioral measures, or a combination of these measures. Physiological measures that are most often used include heart rate or heart rate variability (HRV) and skin conductance (Carter & Tiffany, 1999; Cooney et al., 1997; Waters, Carter, et al., 2009).

Cue sensitivity may also be measured subjectively and is often defined as increases in craving or the desire for alcohol after encountering alcohol-related cues (e.g., Bohn, Krahn, & Staehler, 1995; Schulze & Jones, 2000). Finally, another indicator of cue sensitivity is attentional bias, i.e. a selective focus on alcohol-related cues. Attentional bias is assessed with a reaction time task assessing the extent to which alcohol-related cues are selectively attended to as compared to neutral cues (Field & Cox, 2008).

Methods

A literature search was conducted using PubMed, EMBase/Medline, Web of Knowledge, and PsycINFO, covering all articles published until September 2013. We used the following key terms: alcohol* and ethanol*; cue*, trigger*, stimuli; stress*, ACTH, CRF, cortisol, HPA, and distress; reactivity, sensitivity, cognitive bias and implicit cognition. A total of 12 articles were selected (Figure 1).

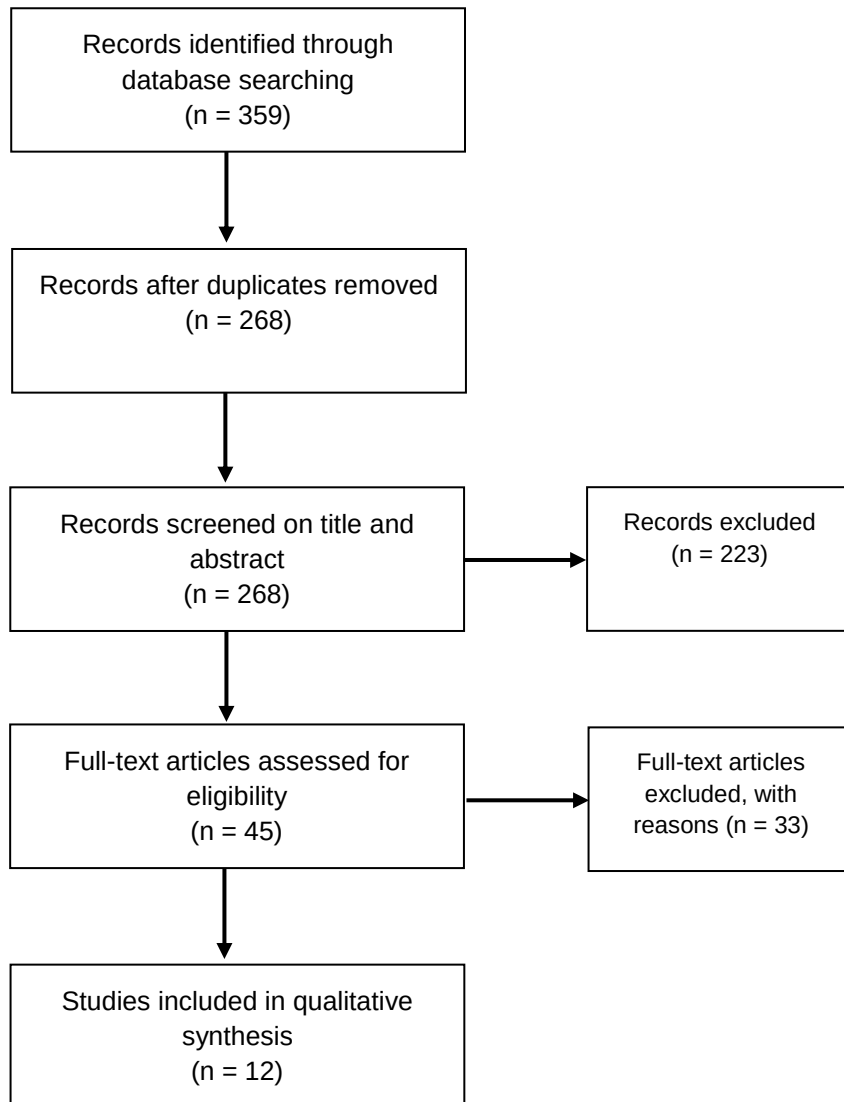


Figure 1. Search strategy and selection process of articles in review

Results

The number of identified eligible studies for this review was relatively small and study samples were diverse. Therefore, we opted for a descriptive synthesis of the results including a calculation of effect sizes. Characteristics of the 12 included articles are presented in Table 1.

We found three global categories of studies based on their design. Studies in category one used experimental within-subjects designs. These designs are the best test of causal relationships and therefore provide the strongest evidence. The second strongest category includes experimental studies using between-subjects designs. These studies are considered to provide somewhat weaker evidence than category one, because participants are exposed to only one mood induction condition. The third category with the weakest evidence includes correlational studies from which no causal inferences can be made.

Table 1. Summary of selected articles for the effect of stress on cue sensitivity

Study	Sample	Type of mood induction	Type of cue exposure	Study design	Results on effect of stress on cue sensitivity
Coffey et al (2006)	43 outpatients with comorbid AD and PTSD	Personalized trauma imagery script vs. neutral script	Sight and smell of participant's preferred alcoholic beverage vs. bottled spring water	Within-subject design. CS measures: craving	Craving increased when confronted with trauma and alcohol cues compared to neutral mood and alcohol cue combination (Cohen's $d = 0.86$)
Field & Powell (2007)	44 heavy social drinking students (19 low CM, 25 high CM)	Expectation of giving a speech and being evaluated vs. solving simple anagrams	Alcohol-related vs. neutral pictures during a visual probe task	Between-subject design. CS measure: attentional bias for alcohol-related pictures	in high CM drinkers only, stress induction led to an increase in attentional bias for alcohol-related cues (Cohen's $d = 1.40$), as compared to neutral mood induction (Cohen's $d = 0.18$)
Field & Quigley (2009)	58 heavy social drinking	Expectation of giving a speech and	Alcohol-related vs. neutral pictures	Between-subject design. CS measure: attentional	In high CM drinkers only, stress induction led to an increase in attentional bias for alcohol-related

	students (28 low CM; 30 high CM)	being evaluated vs. solving simple anagrams	during a visual probe task	bias for alcohol-related pictures	cues as compared to neutral mood induction for both attentional engagement (Cohen's $d = 1.39$) and attentional maintenance (Cohen's $d = 0.64$)
Garland (2011), Garland, Carter, Ropes and Howard (2012), Garland, Franken, Sheetz & Howard (2012)	58 abstinent alcohol-dependent patients, in treatment	Looking at aversive pictures	Looking at alcohol-related pictures	Correlational design. CS measure: change in craving pre- to posttest	There was a significant correlation between change in stress and change in craving, when comparing baseline and post-alcohol cue exposure (Pearson's $r = 0.57$)
Garland et al (2010)	53 abstinent alcohol-dependent patients in treatment	Looking at aversive pictures	Looking at alcohol-related pictures	Between-subject design, with correlational outcome. Mindfulness therapy vs. standard support group therapy (random allocation),	A reduction of stress after 10 weeks of mindfulness (Cohen's $d = 0.74$) accompanied a reduced attentional bias for alcohol-related cues Cohen's $d = 1.03$.

				CS measure: dot-probe task both pre and post treatment	
Jansma et al (2000)	40 abstinent inpatient alcoholics	All participants: neutral mood induction: reading a family magazine. Half of participants distressed induction. Other half: depressing induction	Pouring a glass from a bottle of alcohol and sniff the glass five consecutive times. No neutral cue	Combined within and between-subject design. CS measures: desire to drink, blood pressure, and heart rate variability	Alcohol cue sensitivity was found, but not dependent on mood. Cue sensitivity was not higher when distressed or depressed as compared to a neutral mood for all measures: Desire to drink: Cohen's d = 0.15 Heart rate variability: Cohen's d = 0.00 Blood pressure: Cohen's d = 0.11
Nesic and Duka (2006)	32 heavy social drinking students	Prepare and deliver a 5- min speech followed by a mental arithmetic	Holding and smelling the participant's preferred alcoholic beverage	Between-subjects design. CS measures: skin conductance and desire for alcohol, measured after stress manipulation and after alcohol cue exposure	Overall effects of cue exposure were found for mild desire (Cohen's d = 1.16) and strong desire (Cohen's d = 1.28). However, there was no difference in desire for alcohol after cue exposure between the stress

		task. Control condition: looking at an art history book, assessing paintings and completing dot-to-dot pictures			and control condition (Cohen's $d = 0.39$). Skin conductance increased in non-stressed females (Cohen's $d = 2.01$), but not in stressed males (Cohen's $d = 0.37$), and females (Cohen's $d = 0.73$), and in non-stressed males (Cohen's $d = 1.97$)
Nosen et al (2012)	108 treatment-seeking adults with comorbid PTSD and alcohol dependence	Trauma imagery (narrative description of person's worst traumatic event) vs. neutral imagery (narrative about changing a light bulb)	Alcohol cue was the participant's preferred beverage. Neutral cue was a bottle of water.	Within-subjects design. CS measures: positive and negative affect, and alcohol craving. All participants underwent four counterbalanced imagery-cue combinations: neutral-neutral (NN), trauma-neutral (TN), neutral-alcohol (NA) and trauma-alcohol (TA).	There was a significant difference in alcohol craving after trauma imagery followed by alcohol cues as compared to neutral mood followed by alcohol cues (Cohen's $d = 0.41$)

Pratt and Davidson (2009)	74 non-treatment seeking alcohol-dependent adults whose preferred beverage was beer	Stress was induced using the Paced Auditorial Serial Addition Test (PASAT). Neutral condition was sitting quietly for the same length of time as the PASAT	Neutral cue was water. Alcohol cue was preferred beer brand in a glass behind a sliding door, when accessible, one could drink the beer	Within-subject design. CS measure was craving	There were no significant differences in alcohol craving between stress and neutral condition after cue exposure (Cohen's $d = 0.108$)
Ray (2011)	64 non-treatment seeking heavy drinkers	Stress imagery of stressful recent personal events; neutral	Exposure to water and alcohol beverages	Within-subject design. CS measure was craving	Presentation of alcohol cues increased alcohol craving and negative mood across both stress and neutral imagery. Alcohol cues produced greater increases in craving after neutral imagery when

imagery of
recent
neutral
personal
events

compared to stress imagery
(Cohen's $d = 1.83$)

Note. AD = alcohol dependence, CM = coping motives, CS = cue sensitivity, PTSD = posttraumatic stress disorder

Category 1

In the first category (N = 5), participants were exposed to both a stress and a neutral mood induction. Stress was induced by either using imagery (exposure to emotion-eliciting material) or performing a high-speed task (cognitive task). Cues were presented in vivo by the sight and/or smell of the preferred beverage (Coffey, Stasiewicz, Hughes, & Brimo, 2006; Jansma, Breteler, Schippers, De Jong, & Van Der Staak, 2000; Nosen et al., 2012; Pratt & Davidson, 2009; Ray, 2011).

Coffey et al. (2006) found that participants reported greater craving after trauma imagery followed by an alcohol cue than after trauma imagery followed by a water cue, or after neutral imagery followed by either an alcohol cue or a water cue. These results indicate that trauma-induced stress and exposure to alcohol cues increases craving as compared to neutral mood states and alcohol cues.

Similar results were obtained in another study (Nosen et al., 2012). The greatest increases in craving and salivary flow were observed after trauma imagery was followed by an alcohol cue and these increases were larger than after neutral mood induction and alcohol cue exposure. Both studies support our hypothesis.

Jansma et al. (2000) found that in all conditions (mood induction: distressed, depressed, neutral), heart rate was lower, and heart rate variability, blood pressure and self-reported desire to drink were higher during alcohol cue exposure than during each mood induction; this hints towards an overall alcohol cue sensitivity¹. However, there were no differences in alcohol cue sensitivity measures between conditions. Therefore, this study does not support our hypothesis: the changes induced by exposure to alcohol-related cues were not affected by negative or distressed moods.

In a study conducted by Ray (2011), the results showed that in both mood groups, alcohol cues increased the urge to consume alcohol. In contrast to our hypothesis, alcohol cues produced greater increases in the urge to drink in the neutral mood condition than in the stressed mood condition.

¹ Because of the lack of a non-alcohol cue condition, we cannot be certain of an alcohol specific effect.

Finally, in the study by Pratt and Davidson (2009), there were no significant differences in craving between the stress and neutral mood condition. This indicates that stress did not lead to increased cue sensitivity, in contrast to our hypothesis. However, the authors of the study suggested that this finding may have been caused by a ceiling effect, since craving rates in all conditions were relatively high. Alternatively, craving was measured after alcohol consumption, which we believe may have had an attenuating effect on craving.

In sum, two studies in category one provided evidence that supported our hypothesis that stress affects cue sensitivity (Coffey et al., 2006; Nosen et al., 2012), whereas the remaining three studies did not (Jansma et al., 2000; Pratt & Davidson, 2009; Ray, 2011).

Category 2

All studies in the second category (N = 3) used stressful tasks (i.e., giving an oral presentation that would be evaluated, a public speaking task with verbal interaction) to induce stress in addition to either in vivo presentation of alcohol-related cues including physiological and subjective measurements of cue sensitivity (Nesic & Duka, 2006), or an attentional bias task that exposed participants to alcohol-related pictures (Field & Powell, 2007; Field & Quigley, 2009).

Two separate studies were almost identical in the type of sample selected, study design and recorded measures. In both studies, an attentional bias for alcohol-related pictures was observed only after exposure to the stressor, but not after neutral mood induction. However, this effect was found only in the group of heavy social drinkers whose primary drinking motive was 'drinking to cope'. Thus, these studies support our hypothesis, but only in a subset of drinkers.

In the third study (Nesic & Duka, 2006) both groups exhibited increased skin conductance during cue exposure and increases in craving after cue exposure, indicating overall cue sensitivity. However, no differences were found in craving between the stress and neutral condition. Effects of stress on skin conductance differed between male and female participants: in males, no differences were found between the stress and the neutral condition, whereas in females, skin conductance increased during alcohol cue exposure only in the neutral condition. Thus, this study did not support our hypothesis.

Of the three studies of this category, all of which included heavy social drinkers, two supported our hypothesis. The two supporting studies (Field & Powell, 2007; Field & Quigley, 2009) however, reported effects in coping drinkers only.

Category 3

In the correlational studies of the third category (N = 2, reported in four articles), all participants were exposed to a stress induction, but there was no neutral mood induction. Stress was induced by looking at aversive pictures (exposure to emotion-eliciting material) and cues consisted of alcohol-related pictures. Cue sensitivity was assessed by measuring changes between subjective pre-stress induction and post-cue exposure craving (Garland, 2011; Garland, Carter, Ropes, & Howard, 2012; Garland, Franken, Sheetz, & Howard, 2012) or using an attentional bias task (Garland, Gaylord, Boettiger, & Howard, 2010).

In the first study, which was cited in three articles (Garland, 2011; Garland, Carter, et al., 2012; Garland, Franken, et al., 2012), the results demonstrated an increase in self-reported stress from pre-stress induction (i.e. before stress induction and cue exposure) to post-exposure (i.e. after cue exposure) and a simultaneous increase in craving. Both stress and craving were measured before stress induction and after cue exposure but not in between. Therefore, these results provide correlational evidence supporting our hypothesis: there is evidence that increased stress is associated with increases in craving after cue exposure in alcohol-dependent patients.

The second study (Garland et al., 2010) was selected because of an embedded stress induction and cue exposure paradigm. The paradigm was used before and after treatment (10-week interval). In this study, reduced levels of stress after mindfulness training co-occurred with reduced attentional bias. This study indicates that stress levels may affect sensitivity to alcohol-related cues.

Three of the four articles describe the results of a single study (Garland, 2011; Garland, Carter, et al., 2012; Garland, Franken, et al., 2012) and all articles in this category provide correlational evidence supporting our hypothesis. Because of the nature of correlational designs, we cannot draw conclusions about the causal relationship between stress and cue sensitivity. We can infer, however, that changes in stress levels and cue sensitivity measures are associated.

Discussion

In the present review, we examined evidence supporting the relationship between stress and cue sensitivity. Overall, we conclude that the relationship between stress and cue sensitivity seems to exist; however, it is complex. Mixed results were reported in the review studies. We observed that stress increased cue reactivity in 6 of 10 studies (reported in 12 articles). Our hypothesis was supported mostly by experimental between-subjects studies (category 2; $N = 2$) and correlational studies (category 3; $N = 4$) with medium to large effect sizes. However, it should be noted that these designs are considered to be weaker than experimental within-subjects studies (category 1) in their ability to infer causal relationships. Of the studies using within-subjects designs, three did not support our hypothesis whereas two (one of medium effect size, one large) did support it. It is noteworthy that the two supporting studies from category 1 sampled patients with comorbid PTSD and that the two supporting studies from category 2 found effects in coping drinkers only. Thus the four experimental studies that supported our hypothesis all studied specific groups of participants.

Considering the positive findings reported by within-subjects and between-subjects studies, it appears that stress-induced cue sensitivity exists in coping drinkers and alcohol-dependent patients with PTSD. Individuals of the latter group are likely to comprise mostly coping drinkers as well. Often, people with PTSD may become dependent on alcohol because of its rewarding properties to reduce stress and negative affect (Dixon, Leen-Feldner, Ham, Feldner, & Lewis, 2009; Stewart, Mitchell, Wright, & Loba, 2004; Ullman, Filipas, Townsend, & Starzynski, 2006). Thus, these people can be viewed as drinking to cope with negative affect. Therefore coping drinking seems to be a moderating factor in the relationship between stress and cue sensitivity.

Using the present review as a basis, it appears that stress induced via exposure to emotion-eliciting material, i.e., psychological stress, led to increased cue sensitivity, while stress induced via cognitive tasks, i.e., physical and psychological stress did not. This finding may be explained in light of the Affective Processing Model of Negative Reinforcement (Baker et al., 2004) as referred to in the introduction. Exposure to emotion-eliciting material evokes more negative affect as compared to cognitive induction tasks, the latter evoking more physical stress and arousal. Therefore, it could be that the exposure to emotion-eliciting material evokes negative

affective states comparable to those that were alleviated by drinking in the past (i.e. drinking to cope; Cooper, 1994). As a conditioned effect, when confronted with this type of affect one is motivated to alleviate this by drinking, which enhances the rewarding properties of alcohol cues and thus cue sensitivity.

On the other hand, cognitive tasks evoke more physical stress and an acute arousal state. These states may be evoked less often in daily life. Furthermore, because of their more transient nature they have less likely been alleviated by drinking as a coping mechanism. Therefore, we believe that the conditioned effect that occurs in coping drinkers after psychological stress is unlikely to occur to the same extent after acute physical stress. In general, these acute stress states thus have no significant link with past drinking and therefore do not enhance cue sensitivity.

In future research, the type of stress of interest should be considered. Based on the above, we would suggest that evoking negative states that have been paired with drinking in the past is more important in alcohol cue sensitivity than acute arousal states that are less frequent in daily life and were not often accompanied by drinking. To examine the effect of physical and psychological stress on cue sensitivity, three types of measures should then be incorporated: self-report measures, physiological measures and attentional bias measures. In this review, we reviewed studies using one or two of these types of measures, but not a single study used all three types of measures. In addition, the role of coping drinking should be examined in detail, to investigate whether coping drinking plays a role in the relationship between stress and cue sensitivity.

Since there are not many studies yet with a strong study design, there is a clear need for replication, rendering our conclusions tentative. There may be different factors at play. Our review points toward (1) differences between the effect of psychological stress and physiological stress on cue-sensitivity, and (2) individual differences regarding coping drinking which may explain stress-induced cues sensitivity. We conclude that the relationship between stress and sensitivity to alcohol cues appears to exist, most noticeably in people who drink to cope with negative affect.

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Chapter 4: Attentional bias and approach/avoidance tendencies do not predict relapse or time to relapse in alcohol- dependency

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Abstract

Background: Implicit processes such as attentional bias and automatic approach/avoidance tendencies play a role in substance use disorders. Whether these processes can predict a relapse in alcohol-dependent patients is still unclear and must be examined in more detail than has been done previously. We aimed to establish whether attentional bias and approach/avoidance tendencies measured during treatment would predict relapse in alcohol-dependent patients. We also investigated whether these implicit processes predicted time to relapse better than a more common binary relapse variable.

Methods: A total of 50 alcohol-dependent outpatients undergoing treatment completed the study. Patients completed the Addiction Stroop Task, which assesses attentional bias, and the Stimulus-Response Compatibility Task, which measures approach/avoidance tendencies. Time to relapse was assessed one, two, and three months after the bias assessment.

Results: Twenty patients (40%) relapsed during the follow-up period. The average time to relapse was 40 days after the first session. Overall, participants had an attentional bias for alcohol-related stimuli and a tendency to avoid these stimuli. Neither relapse nor time to relapse was predicted by either bias type.

Conclusions: Although both attentional bias and avoidance tendencies were present in our sample, these measures did not predict relapse or time to relapse in an outpatient alcohol-dependent sample in the following three months. Future research should focus on studying the predictive value of these biases in the short-term, for example, by using ecological momentary assessment techniques to assess implicit processes shortly before a relapse.

Introduction

Implicit processes have become a major field of interest in the study of substance use. So far, we know that both attentional bias (AB; i.e., selective attention for substance-related stimuli or cues) and approach/avoidance tendencies (AA; i.e., the tendency to move toward or away from substance-related cues) each play a role in substance use disorders (e.g., Mogg et al. 2005; Roefs et al. 2011). Several theoretical models have explained how these biases may play a causal role in the onset, maintenance, and/or recurrence of substance use disorders after a period of abstinence (Wiers et al. 2007; Franken 2003; Garland et al. 2011; Tiffany 1990).

Because of attentional bias toward substance-related cues, exposure to these cues eventually increases, which triggers learned responses to the cues. Some of these learned responses represent other implicit processes. One, for example, is related to the motor system: the tendency to move toward or away from substance-related cues, i.e., approach/avoidance tendencies (Garland et al. 2011). Attentional bias can be assessed using computerized tasks such as the Addiction Stroop (Cox et al. 2006), while approach/avoidance tendencies are assessed with computer tasks measuring whether movements, symbolic or actual, toward substance-related stimuli are faster than toward neutral stimuli (e.g., Cousijn et al. 2011; Field et al. 2005; Schoenmakers et al. 2008).

Despite the current knowledge, the clinical relevance of AB and AA remains unclear. Both Field et al. (2014) and Christiansen et al. (2014) concluded in their narrative reviews that AB for substance-related cues is a reliable feature of substance use disorders. Those authors, however, did not recommend assessing AB in treatment settings, for example, to identify those at risk for relapse, because the available evidence is still ambiguous. Studies measuring AB for alcohol-related stimuli during treatment have either shown that AB predicts relapse after discharge (Garland et al. 2012) or failed to find this relationship altogether (Field et al. 2013).

There are currently no published review articles on the clinical relevance of AA because there have been few such studies conducted in the field. However, evidence exists that alcohol-related stimuli can trigger approach tendencies in heavy drinkers (e.g., Field et al. 2008; Palfai & Ostafin 2003; Ostafin & Palfai 2006; Wiers et al. 2009). Additionally, there seems to be a positive association between pretreatment drinking levels and approach tendencies in recently detoxified alcohol-dependent patients

(Barkby et al. 2012), but it remains unclear whether approach tendencies or avoidance tendencies are predictive of subsequent relapse.

To our knowledge, only one published study has assessed the predictive value of AA as measured during treatment on the occurrence of post-treatment relapse (Spruyt et al. 2013). In this study, the Stimulus Response Compatibility Task (R-SRC Task; De Houwer et al. 2001) was used in an alcohol-dependent sample undergoing treatment. R-SRC bias scores were predictive of relapse three months later. Specifically, participants who showed a tendency to *avoid*, not approach, alcohol-related pictures had an increased likelihood of relapsing (Spruyt et al. 2013). The authors proposed that alcohol-dependent patients who abstain may develop avoidance tendencies during early abstinence. Successful relapse prevention requires in-depth emotional processing of alcohol-related cues, making alcohol-related memory structures available for modification. This in-depth processing is not possible when alcohol-related cues are being avoided, keeping the maladaptive alcohol-related memories intact and encountering alcohol-related cues will activate these maladaptive memories, increasing the risk of craving and relapse. This idea, however, contrasts with findings from avoidance-training studies in which training patients to avoid alcohol-related stimuli resulted in reduced relapse rates (Eberl et al. 2014; Wiers et al. 2011; Eberl et al. 2013).

Until now, there is still no gold standard measure of relapse. There are various ways to define and to measure relapse. For example, relapse can be defined as returning to pretreatment drinking levels or as having a binge episode (i.e. having more than 4/5 standard drinks on a single occasion). Relapse is most often measured dichotomously, that is, a patient either relapsed or not. A number of possible measures have been proposed, for example assessing the number of drinking days or the amount of alcohol consumed per drinking day, or a combination of these quantity and frequency measures (e.g. Marlatt and Witkiewitz, 2010). An alternative approach is to measure relapse in a continuous way, by assessing how many days a patient was abstinent prior to the relapse (Fuller, 1997). Christiansen et al. (2014) has recommended to use time to relapse as outcome measure because it seems more appropriate from a clinical perspective. For instance, patients with a severe alcohol use disorder (AUD) often have a greater risk of relapse and of relapsing more quickly than patients with a mild or moderate AUD (e.g., Moos & Moos 2006). Therefore, if we can use AB and AA to predict the amount of time before relapse, it

should be a better indicator of treatment progress or success. A greater number of abstinent days would mean more treatment progress or even long-term treatment success. From a methodological perspective, it also makes sense to use a continuous outcome measure because this increases statistical power, as Christiansen et al. (2014) suggested (also see Fuller, 1997).

Therefore, the purpose of the current study was to investigate whether AA and/or AB can predict relapse in a sample of abstinent alcohol-dependent patients undergoing treatment. The second aim of this study was to investigate whether time to relapse is a better outcome measure for relapse than a binary yes-no variable.

We hypothesized that AB for alcohol-related cues would be present in abstinent alcohol-dependent patients and predict relapse. We also hypothesized that a greater attentional bias would be predictive of a quicker relapse. Furthermore, we expected to find a relationship between AA and relapse. Specifically, based on the findings from Spruyt et al. (2013), we predicted that abstinent alcohol-dependent patients undergoing treatment would tend to avoid alcohol-related stimuli and that this avoidance tendency would predict relapse. Finally, we expected that greater avoidance of alcohol-related stimuli would be associated with a quicker relapse.

Methods

Participants

Participants ($n = 61$) were recruited from three locations of an addiction treatment facility in the Netherlands. Two participants dropped out of the study before all data were collected. Our final sample consisted of 59 participants. Patients were eligible for the study after they had been abstinent from alcohol for at least two weeks. Recruitment took place in an outpatient detoxification program. This program consisted of 6 weeks of therapy, during which patients attended two group therapy sessions per week. The group sessions were led by two counselors who employed cognitive behavioral therapy and motivational interviewing techniques during these sessions. After this six-week program, patients would continue with group therapy, terminate treatment, or start an individual treatment trajectory.

The counselors of the treatment program determined whether a patient was eligible for the study based on our inclusion criteria. Inclusion

criteria were the following: (a) a current diagnosis of alcohol dependence as defined in the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV; American Psychiatric Association 2000) and as determined by Section J of the Dutch version of the *Composite International Diagnostic Interview* (CIDI; World-Health-Organization 1997); (b) an eighth-grade literacy level; and (c) a period of abstinence of at least two weeks prior to the first appointment of the study. Patients were excluded if they: (a) were diagnosed with an Axis II disorder according to the DSM-IV; (b) were diagnosed with a disorder in the psychotic spectrum; or (c) used other addictive substances (except nicotine) on a regular basis.

All participants provided informed consent before the start of the study. The Medical Ethical Committee declared that the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO) does not apply to this research proposal. The Medical Ethical Committee had no objection to the execution of this research.

Study Procedure

The study presented here was part of a larger parent study, the procedure of which was as follows: Eligible patients were referred to the researcher by their counselor. The researcher then contacted the patient to explain the study in more detail and to provide an information leaflet about the study. The researcher contacted the patient again after one week to set up a first appointment.

The study consisted of two similar face-to-face sessions, scheduled four weeks apart during which computer tasks were administered that measured AB and AA. A questionnaire on background variables (see table 1) was administered in the first session, before the computer tasks.

The first face-to-face session took place after the patient had been abstinent for at least two weeks. This two-week period was chosen to ensure that the participants did not experience any withdrawal symptoms during the sessions.

After completing the second session, participants received a financial compensation of €25. Our follow-up regarding the occurrence of relapse took place by telephone both one and two months after session 2.

Implicit measures

Attentional bias

The Addiction Stroop Task (AST) was employed as a measure of AB (Cox et al. 2006) and was administered on an HP iPAQ Pocket PC running the Microsoft Windows Pocket PC operating system in the same format as used by Waters and Li (2008). The iPAQ uses a pen-based touchscreen system. The AST was programmed on the iPAQ to familiarize participants with using this device for a subsequent study (Snelleman et al., in preparation) and has been administered successfully on an iPAQ (Waters & Li, 2008; Waters, Marhe, & Franken, 2012). In this task, words are presented on a screen in three different colors: red, green, and blue. Participants are instructed to ignore the meaning of the words and indicate in which color the word is shown by pressing the correct button on the screen.

The AST consisted of three blocks of 33 trials each. The first block was the practice block and contained letter strings. The second and third blocks were the critical blocks. One block consisted of neutral words (Dutch equivalents of lamp, glue, computer, tape, pencil, scissors, desk, marker, paper, pen, eraser), while the other block consisted of alcohol-related words (Dutch equivalents of beer, wine, alcohol, cocktail, tequila, cognac, sherry, drink, liquor, gin, café). All words in the critical blocks were matched on word length and number of syllables. The presentation order of the two critical blocks was randomized at each session for each participant.

Approach/avoidance tendencies

The R-SRC Task was used to measure approach bias. The R-SRC has been shown to be a reliable predictor of hazardous drinking (Kersbergen et al. 2014). The R-SRC Task was programmed on a Dell laptop with a 15.4" screen using Inquisit 3.0 (Millisecond 2012). In this task, participants are asked to either approach or avoid alcohol-related pictures by moving a manikin toward or away from these pictures.

The R-SRC Task consisted of two blocks: one approach-alcohol block and one avoid-alcohol block. Each block consisted of 10 practice trials and 56 critical trials. Stimuli consisted of 20 alcohol-related pictures and 20 neutral pictures (soda, water, tea, coffee). The context of the stimuli was either active (i.e., person holding the beverage) or passive (i.e., beverage on a white table). Pictures were presented in the center of the screen with a manikin (12 mm high) positioned 33 mm above or below the picture. Participants were required to categorize the presented pictures by making

an approach response (pressing the up or down key to move the manikin toward the picture) or an avoidance response (pressing the up or down key to move the manikin away from the picture). After making a correct response, the manikin would walk toward the picture (approach) or away from the picture (avoidance) for 1,000 ms. Following an incorrect response, a red cross appeared on the screen for 500 ms, after which the next trial started. The order of blocks was counterbalanced among participants.

Follow-up questionnaire on relapse

Follow-up information regarding relapse was gathered at the second face-to-face session and by telephone interviews one and two months after this second session. All participants were asked whether they had relapsed in the preceding month, how many drinking days they had had, and how much alcohol they had consumed during each drinking day. Relapse was defined as having at least one binge drinking episode. Binge drinking was defined as having four or more (for women) or five or more (for men) drinks on one single occasion (e.g., Corbin et al., 2014). Time to relapse was measured in number of abstinent days from the first face-to-face session until the day the participant relapsed.

Statistical analysis

The D-measure scoring algorithm (Greenwald et al. 2003) was adapted to calculate the bias scores from the reaction times on the AST and the R-SRC. This algorithm is recommended when there are differences in baseline speed of responding because it protects against cognitive skill confounds. These confounds were likely to be present because our sample contained participants of varying ages and educational levels.

First, response latencies faster than 300 ms or slower than 10 seconds were removed. Next, means and *SDs* of correct latencies per block and a pooled *SD* were calculated. Penalties were then applied for response errors. Response latencies on trials when participants made errors were replaced by the mean of the correct latencies for the relevant task block plus two standard deviations. After applying error penalties, mean response latencies were recalculated for all blocks (approach and avoidance block of the R-SRC Task; alcohol and neutral block of the AST).

R-SRC bias scores were calculated by subtracting the mean latency of the approach block from the mean latency of the avoidance block and

dividing this difference score by the pooled *SD*. A positive score was therefore indicative of an approach bias, while a negative score indicated an avoidance bias. Attentional bias scores were calculated by subtracting the mean latency of the neutral block from the mean latency of the alcohol block and dividing this difference score by the pooled *SD*. A positive AB score thus indicated an attentional bias.

Results

Demographics

For the relapse analyses, we needed confirmation of a relapse having occurred at any time during the three-month follow-up period, or confirmation of abstinence during the full three months. We could not obtain complete three-month follow-up data for 9 participants (15.3%). We have included only those participants with either complete follow-up data or, when follow-up was not complete, relapsed participants without complete follow-up in our analysis. Our final sample for analyses consisted of 50 participants.

Table 1 displays summary statistics for the whole sample ($n = 50$). There were no significant differences between abstainers and relapsers for age, gender ratio, education level, or number of previous treatments (all p 's $> .14$).

Table 1. *Demographic characteristics of study abstainers and study relapsers.*

	Overall (n = 50)		Abstainers (n = 30)		Relapsers (n = 20)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age	48.7	10.7	50.3	11.5	48.5	9.8
Proportion men (in %)	77.8	-	75.0	-	66.7	-
Educational level (in %)						
<i>High school</i>	24.0	-	20.0	-	30.0	-
<i>Vocational education</i>	30.0	-	40.0	-	15.0	-
<i>Higher vocational education</i>	22.0	-	16.7	-	30.0	-
<i>University</i>	18.0	-	16.7	-	20.0	-
<i>Other</i>	6.0	-	6.7	-	5.0	-
Daily alcohol consumption	20.0	14.9	17.8	14.8	22.8	15.0
Number of previous treatments	1.1	1.4	0.8	0.8	1.6	1.9

Relapse

In total, 20 participants relapsed during the three-month follow-up period. Time to relapse was measured in days, with the mean time to relapse being 40 days (*SD* = 22.19) after entering the study. Seven of those 20 participants had relapsed prior to session 2, therefore all prospective analyses including data from session 2 were conducted without these early relapsers.

Attentional bias

Table 2 describes the mean D-measure scores for the AST per group (abstainers vs. relapsers) for both sessions. Data from two participants (abstainers) at session 1 and data from one abstaining participant at session

2 were incomplete due to a technical malfunction of the PDA and were therefore not included in the analysis. Overall, AB was present in the whole sample at session 1 ($t(47) = 6.169, p < .001$). However, there were no differences in AB between relapsers and abstainers at session 1 ($t(46) = 0.591, p = .558$, Cohen's $d = .17$).

At session 2, AB was still present in the whole sample ($t(41) = 2.52, p = .02$). However, there were no differences in AB between relapsers and abstainers at session 2 ($t(40) = -0.62, p = .54$, Cohen's $d = .07$). Analyses using mean reaction time scores yielded similar results.

Table 2. *D-measure mean scores per group per task per session*

	Overall			Abstainers			Relapsers		
	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>
AST session 1	0.314	0.353	48	0.339	0.313	28	0.278	0.408	20
AST session 2	0.140	0.370	42	0.12	0.42	29	0.20	0.24	13
R-SRC session 1	-0.194	0.412	50	-0.181	0.466	30	-0.211	0.331	20
R-SRC session 2	-0.02	0.35	43	0.02	0.37	30	-0.12	0.27	13

Spearman's rho correlation coefficient between AB and time to relapse in the group of relapsers was also not significant ($\rho = -.293, p = .244$). At session 2, correlation coefficients between AA and time to relapse again were not significant ($\rho = -.301, p = .20$). Therefore, we did not perform any additional analyses using time to relapse as an outcome measure. To check whether AB was stable over time, we calculated the association between AB scores at sessions 1 and 2. Pearson's correlation was low ($r = .29, p = .03$), indicating that AB was not a stable trait in our sample. To check whether the stability of AB over time was influenced by patients who

relapsed before session 2, the analysis was repeated without those early relapsers. This resulted in a similarly low correlation ($r = .21$).

Approach/avoidance tendencies

Table 2 presents the mean D-measure scores on the R-SRC by group (abstainers vs. relapsers) for both sessions. Overall, the results revealed a tendency to avoid alcohol-related pictures ($t(47) = -3.261$, $p = .002$). Again, no differences were found between relapsers and abstainers on the AA ($t(46) = 0.248$, $p = .805$, Cohen's $d = .21$).

At session 2, AA was no longer present in the whole sample ($t(42) = -0.43$, $p = .67$). Additionally, there were no differences in AA between relapsers and abstainers at session 2 ($t(41) = 1.26$, $p = .21$, Cohen's $d = .41$). Analyses using mean reaction time scores yielded similar results.

Spearman's rho correlation coefficients between AA at session 1 and time to relapse were not significant ($\rho = -.199$, $p = .40$). At session 2, correlation coefficients between AA and time to relapse again were not significant ($\rho = .205$, $p = .39$). Therefore, no further analyses were performed with time to relapse.

We also checked whether AA was stable over time by calculating the association between AA scores at session 1 and AA scores at session 2. Pearson's correlation was low ($r = .32$, $p = .014$), suggesting that AA was not a stable trait in our sample. To check whether the stability of AA over time was influenced by patients who relapsed before session 2, the analysis was repeated without those early relapsers. This resulted in a similarly low correlation ($r = .31$).

Discussion

In this study, we investigated whether attentional bias and approach/avoidance tendencies could predict a relapse in abstinent alcohol-dependent outpatients. We found no evidence of the predictive value of these measures, even though our subjects did display both biases: an attentional bias and avoidance tendencies. We also explored whether time to relapse would be a more sensitive outcome measure than a dichotomous relapse measure. However, AB and AA were also not predictive of time to relapse in our sample.

These findings are in line with conclusions drawn in the recent review by Christianson et al. (Christiansen et al. 2014). We could not find evidence that either attentional bias or approach/avoidance tendencies

measured during treatment are predictors of relapse in the long-term, in this case three months. However, we also did not find evidence for the suggestion made by Christiansen et al. (2014) that time to relapse may be a better outcome measure, as there was no relationship between time to relapse and AA or AB in our study.

We have partially replicated the results found by Spruyt et al. (2013). Although, like them, we found an avoidance bias in a clinical sample of alcohol-dependent patients using the R-SRC, we did not find evidence of the predictive value of this avoidance bias despite having identical follow-up periods. Additionally, there seems to be a discrepancy between alcoholic patients showing an avoidance bias (this study and Spruyt et al.) and avoidance training having beneficial effects on relapse (Eberl et al., 2013; Wiers et al., 2011). We believe therefore that more research is needed in the underlying mechanisms of avoidance training.

One major difference between our study and that of Spruyt et al. (2013) is that we recruited our subjects from an outpatient facility, whereas Spruyt and his colleagues recruited their sample from an inpatient detoxification facility. Furthermore, although we employed a broader definition of relapse, we obtained lower relapse rates. These differences indicate that the Spruyt study utilized a more severe sample, and further suggest that the severity of dependence may differentially impact the relationship between AA and relapse. Finally, since we measured attentional bias and not attentional control, we were not able to replicate the finding by Spruyt et al. (2013) that the relationship between R-SRC scores and relapse was reliable in those low in attentional control. Future research should investigate the joint contribution of AA and attentional control in relapse. Another suggestion for future research is to examine the joint contribution of AA and AB in predicting relapse.

There was no evidence to support the use of time to relapse as an outcome measure in our sample. This finding, however, should be interpreted with caution. We did find a moderate correlation between AB and time to relapse ($\rho = -.293$), but this correlation was not significant. The correlation between AA and time to relapse was also not significant ($\rho = -.199$), but this correlation is in the same direction as reported by Spruyt et al. (2013). This could be due to too little variation in the outcome measure, time to relapse, or to the small number of relapsers ($n = 20$). Therefore, future studies should further examine time to relapse as an outcome measure in larger samples to further test its relevance. Additionally, we defined relapse

as having at least one binge episode. It is possible that a more stringent definition of relapse would show more distinctive results on AA and AB and their ability to predict relapse. Future research could incorporate multiple measures of relapse (e.g. number of binge episodes, relapse into pretreatment drinking levels, and number of relapses) to test this idea.

One limitation of the current study is the small sample size. Small samples obstruct finding significant small effects. However, our study's aim was to find clinical relevant effects, rather than merely theoretically interesting differences. Clinical relevance would have been demonstrated when effect sizes had been bigger, making it possible to predict relapse on an individual level, or at the very least on very small subsets of patients. Since we did not find evidence for the predictive value of AA and AB in a small sample, we believe that measuring these biases during treatment has no clinical value in the assessment of potential relapse in individual patients. In addition, our study sample was rather homogeneous, because we included patients that had all been referred to the outpatient treatment program. When a study's aim is not clinical, but theoretical, it should be taken into account that small homogeneous samples may also lead to a rather low variance in bias and relapse scores. When one's aim is to detect theoretically relevant effects, a broader range of patients may lead to bigger effect sizes.

Another way forward in this type of research is varying the timing of measurement of AA and AB. The first assessment of AA and AB occurred when participants had been abstinent for at least two weeks. It is possible that early abstinence or treatment alters these biases, obscuring their predictive value. In addition, measuring attentional and approach biases in the clinic and then predicting long-term relapse may not be the best strategy. Both biases can change over time, as we observed in our study. For example, the associations between bias scores from the two face-to-face sessions were weak. The strength of AB and AA can vary with different contexts such as, for example, when one is confronted with situations that are linked to alcohol use. However, with respect to the study procedures, the environment in which the participants were tested was not linked to the use of alcohol. Therefore, attentional and approach biases may be stronger in contexts that are more relevant to common drinking behavior. As such, perhaps we should not measure these biases in a treatment context. Instead, we should consider assessing these biases in a more naturalistic

setting using, for example, ecological momentary assessment (EMA) methods.

Another argument for the use of EMA methods in future research is that monitoring behavior in daily life is more informative of the relapse process as a whole and can shed more light on the short-term predictive value of attentional and approach biases. A study using EMA methodologies has already shown that an attentional bias toward drugs increases just before a relapse in a heroin-dependent inpatient sample (Marhe et al. 2013), indicating that attentional bias may be a more proximal predictor of relapse, as suggested by Field et al. (2014). Future research is needed to investigate this further.

In summary, the present study did not find evidence for the long-term predictive value of attentional bias and approach bias in alcohol-dependent outpatients. Attentional bias and approach/avoidance tendencies for alcohol-related stimuli seem to be a feature of alcohol dependence, but they have little predictive value for relapse in the long-term when measured during treatment. Future research should focus on the short-term predictive value of both attentional bias and approach/avoidance tendencies by adopting EMA methodologies to track these biases and examine their relationships to relapse in daily life.

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Chapter 5: Do coping motives moderate the relationship between anxiety, craving and drinking?

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Abstract

Alcohol-dependent individuals often report drinking to cope with negative affect as their main reason for drinking. Additionally, drinking to cope with negative affect has been associated with trait anxiety and craving, primarily in student samples. To date, no studies have examined the moderating role that drinking to cope plays in the relationship between trait anxiety, craving and alcohol consumption in alcohol-dependent patients. The main aim of this study was to focus on craving during treatment, which is not only intrusive but is also a risk factor for relapse.

Fifty-nine abstinent alcohol-dependent outpatients underwent measurements of drinking to cope with negative affect, craving, trait anxiety, and weekly alcohol consumption before treatment to examine the moderating role of coping motives in the relationship between anxiety, craving and alcohol consumption.

The results showed that drinking to cope moderated the relationship between trait anxiety and craving during treatment: participants who scored high in both drinking to cope and trait anxiety had higher craving scores than those who scored low on drinking to cope and trait anxiety. Unexpectedly, drinking to cope did not mediate the relationship between trait anxiety and pretreatment weekly alcohol consumption.

Trait anxiety and coping motives were not predictive of self-reported pre-treatment drinking levels. However, our results note that the interplay between anxiety and coping motives is related to intensified craving. Therefore, treatment should focus on reducing anxiety levels in coping drinkers to reduce craving and its potential effect on relapse.

Introduction

Many alcohol-dependent patients report that before treatment they consumed alcohol to relieve negative affect. Additionally, alcohol-dependent patients often report that they drink to relieve negative affect (Kushner et al., 2001), which is also known as drinking to cope with negative affect (Cooper, 1994). Drinking as a coping motive can be seen as a form of self-medication (Khantzian, 1997). In addition, alcohol-dependent patients often report that negative affect triggered craving episodes (Snelleman et al., submitted). The Affective Processing Model of Negative Reinforcement (Baker et al., 2004) offers an explanation for these findings: alcohol-dependent individuals respond to negative affect by repeatedly consuming alcohol, which teaches them that alcohol relieves negative affect (i.e., self-medication). Through this repeated use in negative affect situations, associations are formed between alcohol use and relief of negative affect through negative reinforcement. Consequently, alcohol use, or when using alcohol is not possible, craving is provoked when alcohol-dependent individuals experience negative affect.

Craving itself can be intrusive and interfere with daily life in abstinent alcoholics (Tiffany & Wray, 2012); therefore, learning to address craving is an important treatment target. However, not all alcohol-dependent patients report that they experience craving, and when they do, the intensity and frequency of craving episodes vary (Tiffany 1990; Oslin et al. 2009; Snelleman et al., submitted). Thus, it is important to know which patients experience stronger cravings and under which circumstances they experience these cravings. In the current study, we focus on trait anxiety as a type of negative affect (Cheetham, Allen, Yücel, & Lubman, 2010) and its relationship with craving and pre-treatment drinking. In addition, we examine the moderating role of coping motives in this relationship because we expect that alcoholics with strong coping motives are most likely to drink when experiencing negative affect.

Many studies have investigated the relationship between trait anxiety, craving, drinking and coping motives. Most of these studies, however, were conducted in social drinkers and not in samples of alcohol-dependent individuals. For example, it has been shown that in social drinkers and abstinent alcohol-dependent patients, high trait anxiety scores are related to stronger cravings (Litt et al., 2000; Shaver, Veilleux, & Ham, 2013; Sinha et al., 2011). In addition, social drinkers who score high on trait anxiety drink on average more alcohol than social drinkers who score low on trait anxiety (Allan, Albanese, Norr, Zvolensky, & Schmidt, 2015). If the same

finding is true for alcohol-dependent patients, then there are important clinical implications: assessing trait anxiety in patients during treatment would be important as an indication of intense or frequent craving experiences. In addition, if a patient's anxiety contributed to high drinking levels before treatment, the assessment of trait anxiety adds important information to a patient's clinical presentation.

Trait anxiety is related to craving and alcohol consumption, and high trait anxiety is also related to coping motives in adolescents (Comeau, Stewart, & Loba, 2001) and in heavy drinking college students (Kenney, Lac, Labrie, Hummer, & Pham, 2013). Additionally, drinking to cope with negative affect is related to craving. Studies of the relationship between drinking to cope with negative affect and craving showed that social drinkers with high coping motives showed greater increases in alcohol craving after a stressful mood induction than those with low coping motives (Field & Powell, 2007; Field & Quigley, 2009). Unfortunately, these studies incorporated stress, not anxiety, as a type of negative affect. To our knowledge, there are still a few studies examining the relationship between craving, anxiety and drinking to cope with negative affect.

As previously stated, anxiety, as a type of negative affect, has also been associated with alcohol consumption. Some studies have examined the role of drinking motives and anxiety in predicting alcohol problems. One study has shown that both generalized anxiety and drinking to cope predict alcohol problems in a nondependent community sample (Allan et al., 2015). Goldstein and Flett (2009) tested the interaction between trait anxiety and coping motives. Their study showed that in adolescents with high coping motives, increased anxiety symptoms were associated with more alcohol problems.

In sum, many studies have investigated the relationship between coping motives, anxiety and alcohol consumption. Unfortunately, most of these studies included student samples. Additionally, few studies have investigated the relationship between craving and drinking to cope with negative affect in heavy drinking samples. Again, few studies have examined the role of drinking motives in alcohol-dependent patients, and to the best of our knowledge, no study has assessed the moderating role of coping motives in the relationship between trait anxiety, craving and weekly alcohol consumption in alcohol-dependent patients.

The objective of the current study is, therefore, to explore the moderating role of coping motives in the relationship between anxiety,

alcohol consumption, and craving. We hypothesize that there is a positive relationship between trait anxiety and craving in abstinent patients. We also expect that this relationship is moderated by coping motives to drink: patients with high trait anxiety and who endorsed coping motives to drink before treatment will experience the strongest cravings during treatment compared to patients who do not have these coping motives.

Second, we hypothesize that there is a positive relationship between trait anxiety and pretreatment alcohol consumption. Additionally, we expect that this relationship is moderated by coping motives to drink. More specifically, we expect that patients who had high trait anxiety and who also used to drink to relieve negative affect consumed the most alcohol before treatment.

Methods

Participants

Participants (n=61) were recruited from three locations of an addiction treatment facility in the Netherlands. Two participants dropped out of the study before the data collection was completed. Our final sample consisted of 59 participants. The sample characteristics are shown in Table 1.

Table 1. *Sample characteristics.*

	Overall (n = 59)	
	<i>M</i>	<i>SD</i>
Age	48.1	10.5
Proportion men (in %)	72.9	-
Educational level (in %)		
<i>High school</i>	23.7	-
<i>Vocational education</i>	30.5	-
<i>Higher vocational education</i>	23.7	-
<i>University</i>	16.9	-
<i>Other</i>	5.3	-
Number of DSM 5 symptoms	7.9	2.2
Number of previous treatments	2.0	1.8
Mean weekly alcohol consumption	129.5	104.2
Mean no. of drinking days per week	6.4	1.4
Mean no. of drinks per occasion	19.5	14.3
Obsessive Compulsive Drinking Scale	12.2	7.7
State Trait Anxiety Inventory – trait form	46.3	12.7
Drinking Motives Questionnaire Revised – coping motives	3.8	0.7

Patients were eligible for the study after they had been abstinent from alcohol for at least two weeks. Recruitment took place in an outpatient detoxification program. This program consisted of 6 weeks of therapy, during which the patients attended two group therapy sessions per week. All of the group sessions were led by two counselors who employed cognitive behavioral therapy and motivational interviewing techniques during these sessions.

The treatment program counselors determined whether a patient was eligible for the study based on our inclusion criteria: (a) a current diagnosis of alcohol dependence, as defined in the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV; American Psychiatric Association 2000); (b) an eighth-grade literacy level; and (c) an abstinence period of at least two weeks prior to the study appointment. Patients were excluded if they (a) were diagnosed with an Axis II disorder, according to the DSM-IV; (b) if they were diagnosed with a disorder in the psychotic spectrum; or (c) if they used other addictive substances (except nicotine) on a regular basis before treatment.

All participants provided informed consent before the start of the study. The Medical Ethical Committee of the Erasmus Medical Center in Rotterdam declared that the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO) does not apply to this research proposal. The Medical Ethical Committee had no objection to the execution of this research.

Study Procedure

This study was part of a larger study on the predictors of alcohol consumption and craving (Snelleman, Schoenmakers, & van de Mheen, 2015). The larger study consisted of two face-to-face sessions followed by a three-month follow-up period. For the purpose of the current study, only questionnaire data from the face-to-face sessions were needed.

Eligible patients (based on the criteria described above) were referred to the researcher by their counselors. The researcher then informed the patient about the study in more detail and provided an information leaflet describing the study. The researcher contacted the patient again after one week to set up an appointment for session 1.

Session 1 took place after the patient had been abstinent for at least two weeks. This two-week period was chosen to ensure that the participants did not experience any withdrawal symptoms during the sessions. Session 2 was scheduled four weeks after session 1. After completing the second session, the participants received a financial compensation of €25.

Questionnaires

State-Trait Anxiety Inventory

We used the trait form from the Dutch version of the State-Trait Anxiety Inventory (STAI DY, Ploeg, 1982). This questionnaire contains 20 statements, such as *“Generally, I feel nervous and anxious”*. Participants indicate to what degree the statements apply to themselves. Answers are given on a 4-point scale (1=rarely; 2=sometimes; 3=often; and 4=frequently).

Drinking Motives Questionnaire Revised

The Drinking Motives Questionnaire Revised (DMQ-R; Cooper, 1994) assesses which reasons people have for consuming alcohol. It identifies four types of drinking motives: enhancement, coping, social, and conformity. Only the coping motives subscale was of interest to the current study. The coping motives subscale consists of five statements, such as *“I drink alcohol because it helps me when I feel depressed or nervous”*, and the participants indicate on a 5-point scale (1=never; 2=seldom; 3=sometimes; 4=often; 5=always) to what extent each statement applies to their pre-treatment drinking behavior.

Obsessive Compulsive Drinking Scale

The OCDS is a self-report questionnaire that contains questions about obsessive thoughts of alcohol use (e.g., *“How much of your time when you're not drinking is occupied by ideas, thoughts, impulses, or images related to drinking?”*) and compulsive behaviors toward drinking (e.g., *“How much of an effort do you make to resist consumption of alcoholic beverages?”*). These two components are considered to be an important part of the concept of craving (Anton, Moak, & Latham, 1995). The OCDS contains 14 questions about craving during the past seven days, and the participants indicate which of five possible answers apply to themselves. For this study, we used the total score on the OCDS as a proxy for past-week alcohol craving.

Alcohol consumption before treatment

To assess alcohol consumption before treatment, we used data from section J of the Composite International Diagnostic Interview (CIDI; World-Health-Organization, 1997). Two measures of alcohol consumption were obtained:

the mean number of drinking days per week and the number of drinks per drinking occasion during the past twelve months. We multiplied the number of consumed standardized drinks per occasion by the number of drinking days per week to obtain the mean weekly alcohol consumption before treatment (Lemmens et al., 1992).

The mean questionnaire scores are provided in Table 1.

Results

Summary statistics

The participant demographics and the mean scores from the questionnaires are displayed in Table 1. We determined whether any of the demographic variables (e.g., age, gender, educational level, number of symptoms, number of previous treatments) were related to trait anxiety, alcohol consumption, craving and coping motives. Age was negatively associated with weekly alcohol consumption (Kendall's $\tau = -.26$, $p = .005$) and coping motives ($r = -.25$, $p = .03$), indicating that the younger participants had higher levels of pretreatment alcohol consumption and were endorsing coping motives to drink more often than older participants. Because gender was also correlated with pretreatment alcohol consumption (Kendall's $\tau^2 = .37$, $p = .001$), which indicated that the male participants had higher levels of pretreatment alcohol consumption, we decided to correct for age and gender in the regression analyses.

Correlations between the dependent and independent measures are shown in Table 2. Trait anxiety and craving were significantly correlated ($r = .487$), indicating that higher trait anxiety accompanies higher craving. Craving was also correlated with drinking to cope with negative affect ($r = .303$); endorsing coping motives to drink more often is related to higher craving scores.

² Kendall's tau was chosen here because of the non-normal distribution of alcohol consumption and the p-value of Kendall's tau is more accurate when using smaller samples.

Table 2. Correlations between craving, alcohol consumption, trait anxiety, and coping motives

	1	2	3	4
1. Weekly alcohol consumption	-			
2. OCDS	,225	-		
3. DMQ-coping	,180	,303*	-	
4. STAI-T	-,004	,487**	,188	-

Note: OCDS = Obsessive Compulsive Drinking Scale; DMQ-coping = coping motives subscale of the Drinking Motives Questionnaire Revised; STAI-T = trait form of the State Trait Anxiety Inventory; * $p < .05$; ** $p < .01$

Craving during treatment

To test the hypothesis that the relationship between trait anxiety and craving is moderated by coping motives, we performed regression analysis with three predictors: trait anxiety, coping motives, and the trait anxiety x coping motives interaction. All regression coefficients are shown in Table 3. The interaction of trait anxiety and coping motives was significant ($\beta=2.09$, $p=.01$). To interpret this finding, we performed post-hoc analyses using median splits for the variables trait anxiety and coping motives, creating four groups: 1) below the median score for trait anxiety and coping motives, 2) above the median score for trait anxiety and below the median score for coping motives, 3) below the median score for trait anxiety and above the median score for coping motives, and 4) above the median score for trait anxiety and coping motives. Using the Bonferroni correction for multiple testing, these post-hoc analyses showed that the mean craving scores for group 4 (above the median score for trait anxiety and coping motives, $M=18.55$, $SD=5.09$) were significantly higher than the mean craving score for group 1 (below the median score for trait anxiety and coping motives, $M=9.10$, $SD=7.30$, $p=.004$). There were no other between-group differences in the mean craving scores. Thus, higher scores on both measures predicted the highest scores for craving.

Table 3. Regression coefficients showing trait anxiety and drinking to cope as predictors of past week craving.

Variable	<i>b</i> coefficient (95% CI)	β	<i>t</i>	<i>R</i> ²	<i>F</i> change
Step 1				.17	5.87**
Age	-0.30 (-0.48; -0.12)	-0.42	-3.40**		
Gender	-0.08 (-4.28; 4.11)	-0.005	-0.04		
Step 2				.37	8.24 **
Age	-0.22 (-0.38; -0.05)	-0.30	-2.59*		
Gender	0.27 (-3.48; 4.03)	0.02	0.15		
DMQ-CM	1.77 (-0.83; 4.37)	0.40	1.36		
STAI-T	.24 (-1.50; 0.01)	0.15	3.59**		
Step 3				.44	7.04*
Age	-0.19 (-0.35; -0.03)	-0.27	-2.42*		
Gender	0.70 (-2.88; 4.27)	0.04	0.39		
DMQ-CM	-9.35 (-18.12; -0.59)	-0.82	-2.14*		
STAI-T	-0.75 (-1.50; 0.01)	-1.25	-1.98		
DMQ-CM x STAI-T	0.27 (0.07; 0.47)*	2.09	2.65*		

Note: * = $p < .05$; ** = $p < .01$; DMQ-CM = coping motives subscale of the Drinking Motives Questionnaire Revised; STAI-T = trait form of the State Trait Anxiety Inventory.

Alcohol consumption prior to treatment

We also performed regression analyses to test whether coping motives moderate the relationship between trait anxiety and pretreatment alcohol consumption. We found no evidence that trait anxiety predicts pretreatment alcohol consumption or that coping motives moderate the

relationship between trait anxiety and pretreatment alcohol consumption; none of the variables predicted weekly alcohol consumption after controlling for gender and age. All of the regression coefficients are shown in Table 4.

Table 4. Regression coefficients showing trait anxiety and drinking to cope as predictors of weekly alcohol consumption

Variable	b coefficient (95% CI)	β	t	R ²	F change
Step 1				.32	12.88**
Age	-3.98 (-6.20; -1.77)**	-0.40	-		
			3.60**		
Gender	-105.88 (-157.95; -53.80)**	-0.46	-		
			4.07**		
Step 2				.328	0.53
Age	-3.95 (-6.30; -1.61)	-0.40	-		
			3.38**		
Gender	-105.09 (-157.78; -52.40)	-0.45	-		
			4.00**		
STAI-T	-0.79 (-2.67; 1.100)	-0.10	-0.84		
DMQ-CM	13.14 (-23.32; 49.60)	0.08	0.72		
Step 3				.331	0.239
Age	-3.89 (-6.27; -1.52)**	-0.39	-		
			3.29**		
Gender	-103.93 (-157.24; -50.62)**	-0.45	-		
			3.91**		
STAI-T	-3.50 (-14.81; 7.81)	-0.43	-0.62		
DMQ-CM	-17.38 (-147.92; 113.17)	-0.11	-0.27		
DMQ-CM x STAI-T	0.728 (-2.26; 3.71)	0.42	0.49		

Note: ** = $p < .01$; DMQ-CM = coping motives subscale of the Drinking Motives Questionnaire Revised; STAI-T = trait form of the State Trait Anxiety Inventory.

Discussion

In this study, we investigated the moderating role of coping motives to drink with regard to the relationship between trait anxiety and past-week craving levels in abstinent alcoholic patients. As expected, there was a strong relationship between trait anxiety and past-week craving. Additionally, coping motives moderated the relationship between trait anxiety and past-

week craving. The participants who had the highest levels of trait anxiety and drinking to cope experienced the strongest cravings in the past week.

We also investigated whether coping motives would moderate the relationship between trait anxiety and pretreatment alcohol consumption. Contrary to our expectations, we did not observe a relationship between trait anxiety and alcohol consumption. Additionally, there was no moderating effect of coping motives on the relation between trait anxiety and pretreatment alcohol consumption, which was also against our expectations.

As in previous studies (Litt et al., 2000; Sinha et al., 2011), we found a relationship between trait anxiety and craving, and we were able to refine this relationship by showing that coping motives play a moderating role in this relationship. Until now, only relationships between trait anxiety, coping motives, and craving have been established, primarily in nondependent samples (e.g., Comeau et al., 2001; Kenney et al., 2013). Our study expands the current knowledge on this topic and demonstrates that the relationship between trait anxiety and craving is also present in alcohol-dependent patients and that this relationship is moderated by coping motives.

As previously mentioned, we did not observe any moderating effect of coping motives on the relationship between trait anxiety and pre-treatment alcohol consumption. These results are somewhat contrary to the findings from a study by Corbin et al. (2013), who found that coping motives were related to higher levels of weekly alcohol consumption in a sample of undergraduate students. In addition, in a study identifying the different types of college student drinkers, the high risk individuals were characterized by high levels of negative affect, coping motives, drinks per week and drinking-related problems (Holt et al., 2013). However, differences in the samples may explain the discrepant results. In our study, the whole sample was drinking heavily prior to treatment, whereas in the Corbin et al. and Holt et al. studies, undergraduates and college students were included if they reported any alcohol consumption in the last three months, thereby leading to greater variations in weekly alcohol consumption compared to a sample of alcohol-dependent patients who were drinking heavily before entering treatment.

An alternative explanation for our results may lie in the timeframe to which the utilized measures refer. Pretreatment alcohol consumption concerned the previous twelve months (before treatment), whereas the occurrence and strength of craving concerned the past week (during treatment). Although trait anxiety and coping motives were assessed as trait

variables, being in treatment may have altered the participants' self-reported trait anxiety and coping motives. In addition, coping motives may not be stable but rather dynamic, and changes in coping motives may predict differential drinking patterns (Dvorak, Pearson, & Day, 2014). Therefore, if the coping motives in our sample had been different during treatment than before treatment, both factors (i.e., coping motives and pretreatment alcohol consumption) would have concerned different time periods, thereby decreasing their correlation.

We were unable to find a direct relationship between trait anxiety and pretreatment drinking levels in our sample. This finding contrasts with previous studies that have shown that trait anxiety is related to alcohol consumption in psychiatric populations (Thornton et al., 2012). However, anxiety was measured when the participants had been abstinent for at least two weeks, while research has shown that anxiety symptoms decrease in abstinent alcohol-dependent patients during treatment (e.g., Kushner et al., 2013), possibly explaining why we did not find a direct relationship between trait anxiety (measured during treatment) and pretreatment alcohol consumption. Another possibility is that ceiling effects affected our results. All participants drank heavily prior to treatment, leading to less variance in the alcohol consumption measure, making it more difficult to find significant results.

Craving during treatment appears to be stronger when levels of trait anxiety and drinking to cope with negative affect are high. Because patients with low levels of craving are most successful in maintaining abstinence (Oslin et al., 2009), efforts should be made to reduce craving; in addition, craving can be very intrusive and distressing (Tiffany & Wray, 2012). When reviewing our results, one method of achieving this goal is to screen new patients for trait anxiety and coping motives at the beginning of treatment. Reducing anxiety levels in coping drinkers may be an effective strategy to reduce craving in alcohol-dependent patients who have high levels of trait anxiety.

In sum, we found evidence supporting the moderating role of coping motives in the relationship between trait anxiety and craving. We failed to demonstrate that coping motives play a moderating role in the relationship between trait anxiety and pretreatment alcohol consumption.

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Chapter 6: Craving and affect among alcohol-dependent patients trying to maintain abstinence: An Ecological Momentary Assessment study.

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Abstract

Craving is a central phenomenon in addiction, yet little is known about the natural history of craving in alcohol-dependent outpatients. This study examined the natural history of temptation episodes in alcohol-dependent patients. We also examined affective correlates of temptation episodes, and compared patients who relapsed and those who remained abstinent.

Using personal digital assistants (PDA's), 43 alcohol dependent outpatients were signaled to complete assessments three times a day (random assessments, RAs). They were also instructed to complete an assessment when they experienced craving for alcohol or came to the brink of drinking without doing so (temptation assessments, TAs). Data was collected during four weeks. Assessments included current craving, current positive and negative affect, current and past-hour stress, and current motivation to remain abstinent.

Craving, negative affect and stress were higher at TAs than at RAs. Abstinence motivation was lower at TAs than at RAs. Further, the effect of assessment type (TAs vs RAs) on negative affect, stress, and abstinence motivation was greater for relapsers than non-relapsers. Averaged over assessment types, relapsers reported higher craving ratings than non-relapsers.

Temptation episodes in alcohol-dependent patients were characterized by elevated craving, stress and negative affect. This elevation was greater in relapsers, suggesting that temptation episodes may be more severe for relapsers. Further research is required to clarify the causal pathways linking craving/temptations, affect, and relapse.

Introduction

Many substance use disorder patients (SUDs) frequently report the experience of cravings when they are abstaining from substance use (Epstein et al., 2009). In studies with alcohol-dependent individuals, however, overall craving ratings are often low and seem to show very little variation over time (e.g. 2–4). Most of these studies have been conducted in the laboratory, so it remains unclear whether alcohol-dependent individuals experience cravings of a different intensity in real-world settings and whether cravings assessed in real-world settings are associated with clinical outcomes.

Recently, addiction researchers have used Ecological Momentary Assessment (EMA) to investigate experiences and behavior in real-world settings (Aan het Rot, Hogenelst, & Schoevers, 2012; Serre, Fatseas, Swendsen, & Auriacombe, 2015; Van Os, Lataster, Delespaul, Wichers, & Myin-Germeys, 2014; Walz, Nauta, & Aan het Rot, 2014). EMA protocols allow for daily monitoring of behaviors of interest in a naturalistic setting using electronic devices. Another feature of EMA is that different types of assessments can be administered. Besides random assessments (RAs; scheduled at random times throughout the day), participants can also be asked to initiate assessments at times of particular interest. In the current study, participants were asked to initiate assessments when they experienced a temptation to drink (temptation assessments, TAs). A temptation can be defined as any occasion when an alcohol-dependent patient, attempting to abstain, experiences an acute increase in the urge to drink alcohol or an occasion when the patient feels tempted to drink alcohol without actually doing so (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). By this definition, temptations may therefore involve craving, but temptations can also occur in the absence of craving.

The EMA approach has been used in studies of smoking (Shiffman, 2009) and heroin/cocaine addiction (Waters et al., 2012). In these studies, TAs were characterized by higher negative affect and stress, at least in cocaine-dependent and heroin-dependent patients (Epstein et al., 2009; Marhe, Waters, van de Wetering, & Franken, 2013), and negative affect was also elevated prior to TAs in smokers (Waters et al., 2014). However, temptation episodes have not been studied in alcohol-dependent patients using electronic devices. Litt et al. (Litt, Cooney, & Morse, 1998) did assess temptation episodes in alcohol-dependent patients, but recording of these

episodes was done using paper-and-pencil methods, resulting in low overall compliance to recording of episodes, possibly biasing the results.

Although temptation episodes have not been widely studied in alcohol-dependent patients using EMA, studies have examined the effect of stress and negative affect on craving (though not temptation episodes) in the laboratory. These studies showed that stress increases negative affect and craving for alcohol in alcohol-dependent patients (Fox et al., 2007; Sinha et al., 2009). Additionally, cue-induced craving led to higher stress and negative affect as compared to exposure to neutral cues in these studies (Fox et al., 2007; Sinha et al., 2009). Overall, laboratory studies suggest that alcohol craving may be associated with elevated negative affect either because craving is elicited by stress or negative affect, or because the experience of craving itself acutely increases stress or negative affect. However, since craving was induced in the lab, we do not know if craving (or temptation episodes) are accompanied by more stress and negative affect in real-life.

Although most research has focused on stress and negative affect, positive affect has also been investigated in laboratory studies. For example, Fox et al. (Fox et al., 2007) showed that positive affect decreased in response to cue-induced craving in treatment-seeking alcohol-dependent patients. On the other hand, inducing positive affect can increase craving in non-treatment seeking alcohol-dependent individuals (Mason, Light, Escher, & Drobles, 2008). These studies showed that the relationship between craving and positive affect may be complex, and deserves further scrutiny.

Another variable that may be important during temptation episodes is the motivation to remain abstinent. However, to our knowledge no studies have examined abstinence motivation during temptation episodes. It is known that motivation drives behavior (e.g. 16,17), and that motivation for abstinence decreases after an initial lapse, a phenomenon called the abstinence violation effect (Curry, Marlatt, & Gordon, 1987; Witkiewitz & Marlatt, 2004). However, it is not known what happens to abstinence motivation when patients experience a temptation episode.

As suggested by the laboratory studies reviewed earlier, craving, and presumably also temptation episodes, are potentially stress-inducing, and so individuals who experience more TAs and who have more negative experiences during TAs may be at greater risk of relapse. Although previous research in other addictions has shown that frequency of temptations is not associated with relapse (Marhe et al., 2013), the “severity” of temptations

(vs. RAs) has been associated with relapse (Marhe et al., 2013). For example, Marhe et al. (Marhe et al., 2013) reported that cocaine-dependent and heroin-dependent participants who reported greater increases in craving at TAs (vs. RAs) were more at risk of early relapse. Therefore, we also examined whether any effect of assessment type (TAs vs. RAs) was moderated by relapse status.

In sum, the goals of the study were as follows. First, using EMA we sought to describe the natural history of temptation episodes in alcohol-dependent outpatients who attempted to remain abstinent. Second, we examined whether stress, abstinence motivation, and negative and positive affect differed between TAs and RAs. Finally, we examined whether any effect of assessment type (TAs vs. RAs) was different in relapsers and non-relapsers.

Methods

Participants

This study was part of a larger study on predictors of relapse and craving (Snelleman et al., 2015). For the parent study, alcohol-dependent patients ($n=59$) were recruited from three locations of an addiction treatment facility in the Netherlands. Recruitment took place in an outpatient detoxification program (Figure 1) which consisted of 6 weeks of group therapy. Of the 59 participants in the parent study, 43 agreed to participate in the current EMA study. Of these 43 participants, 12 continued with group therapy, 3 terminated treatment, and 28 started an individual treatment trajectory. Additionally, participants either used disulfiram ($n=10$), acamprosate ($n=4$), naltrexone ($n=2$) or no medication ($n=27$).

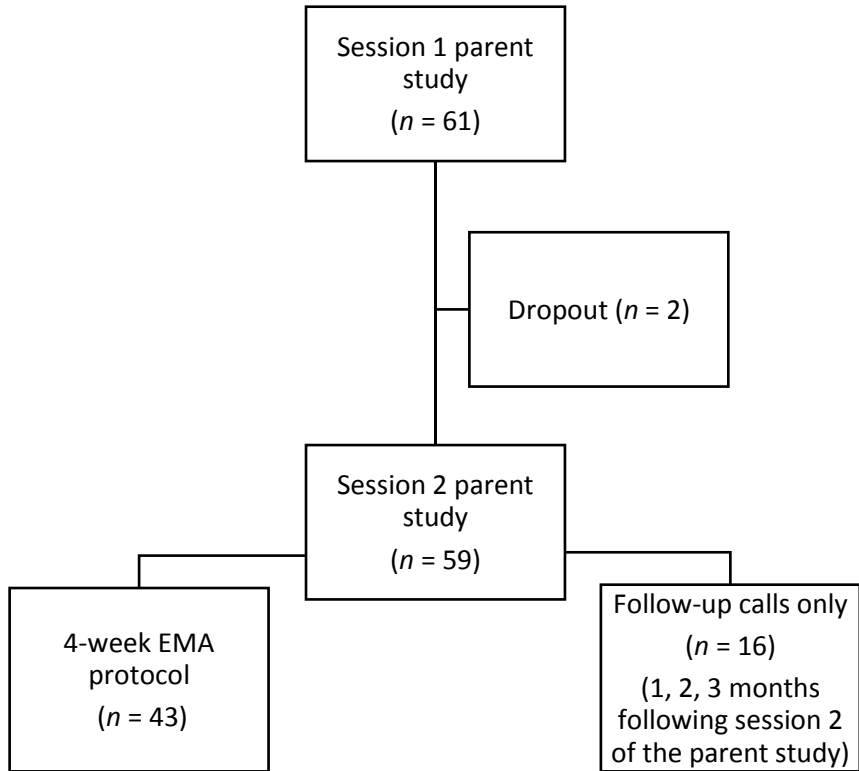


Figure 1. recruitment of participants

Inclusion criteria were the following: (a) a current diagnosis of alcohol dependence as defined in the DSM-IV (American Psychiatric Association, 2000) and as determined by Section J of the Dutch version of the *Composite International Diagnostic Interview* (CIDI;24); (b) an eighth-grade literacy level; and (c) a period of abstinence of at least two weeks prior to the first appointment of the parent study. Patients were excluded if they: (a) were diagnosed with an Axis II disorder according to the DSM-IV; (b) were diagnosed with a disorder in the psychotic spectrum; or (c) used other addictive substances (except nicotine) on a regular basis.

Procedure

The counselors of the treatment program determined whether a patient was eligible for the study based on our inclusion criteria. Eligible patients were referred to the researcher by their counselor and the researcher fully described the study to the patient. Written informed consent was obtained from all participants.

The 43 EMA participants were trained in using a personal digital assistant (PDA) at the first laboratory visit. Thereafter four weeks of EMA started. The PDA was programmed to signal three times a day at random times (RA). Participants were also instructed to start an assessment themselves when they experienced an acute increase in the urge to drink or an occasion when they felt tempted to drink without actually doing so (TA). At each RA or TA, participants responded to items assessing subjective variables (e.g., craving). Subsequently participants were presented with either an alcohol Stroop task or an alcohol approach-avoidance IAT (data not reported here). The median duration of EMA assessments was 4.16 minutes.

Data were downloaded from the PDA and protocol compliance and past-week alcohol consumption were checked by the researcher during weekly face-to-face appointments with participants. Participants continued the study even if they relapsed. After four weeks, participants handed in the PDA and received financial compensation for participation (€4.45 per day, max €125). The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, The Netherlands (registration number MEC-2012-346).

EMA measures

Craving

Craving was assessed using three items: 1) "I feel the urge to drink right now" (Craving), 2) "I feel tempted to drink right now" (Tempted Now), and 3) "In the last hour, I felt tempted to drink" (Tempted Past Hour). Participants indicated whether they agreed with these statements on a 7-point scale (1=*not at all* to 7=*very*).

Positive and Negative Affect

We used the Positive and Negative Affect Schedule – short form (PANAS-SF; Thompson, 2007), which consists of 10 items: five positive (PANAS-PA) and five negative items (PANAS-NA). The PANAS-NA did not contain an item on stress, ensuring no overlap between stress and negative affect. Participants indicated whether they agreed with a statement (e.g., I feel upset right now) on a 5-point scale (1=*not at all* to 5=*extremely*). Cronbach's alpha was good for both PANAS-PA ($\alpha=.90$) and PANAS-NA ($\alpha=.89$).

Stress

Stress was measured using two items: 1) "I feel stressed right now" (Stressed Now); and 2) "In the last hour I felt stressed" (Stressed Past Hour). Again, participants indicated whether they agreed with these statements on a 7-point scale (1=*not at all* to 7=*extremely*).

Abstinence motivation

Motivation to maintain abstinence was measured using one item: "How motivated are you right now to stay abstinent?" (Motivation). Again, participants indicated on a 7-point scale whether they agreed with this statement (1=*not at all* to 7=*extremely*).

Relapse

Participants indicated how many glasses of alcohol they consumed since the previous assessment (1=no drinks; 2=1-2 glasses; 3=3-4 glasses; 4=5-6 glasses; 5=7 or more glasses).

Relapse was defined as an alcohol consumption of at least 5 standard glasses (males) or at least 3 standard glasses (females) since the previous EMA assessment, i.e. the occurrence of at least 1 binge drinking episode since the previous EMA assessment.

Data Analysis

The primary analyses used linear mixed models (LMMs) using SAS PROC MIXED. LMMs take into account dependence between observations due to clustering of data by participants and permit different numbers of

observations across participants. Day in study (continuous variable) was included as a covariate in all models. Alpha was set to .05, and all tests were 2-tailed.

First, we examined the natural history of temptations over the study for all subjects and for relapsers ($n=12$) and non-relapsers ($n=31$) separately. Second, to compare ratings at TAs and RAs (Assessment Type), we used a LMM that included the proportion of completed assessments that were TAs (i.e., no. of TAs divided by total number of assessments, a subject-level variable) as well as Assessment Type. A significant parameter estimate for Assessment Type would reveal a within-subject effect, i.e., when subjects experience a TA they have higher scores on the EMA variable at TAs than at RAs (Hedeker, Mermelstein, Berbaum, & Campbell, 2009). Assessment Type was treated as a random effect in the model (slopes were allowed to vary) if the p-value for the covariance parameter estimate (for Assessment Type) was less than .1 (Fitzmaurice, Laird, & Ware, 2011). These analyses used all 2020 assessments (1870 RAs, 150 TAs).

In the aforementioned analyses, EMA assessments in which prior drinking was reported were included. Because recent drinking could influence responses, we conducted supplementary analyses subsetting to assessments that occurred when participants (relapsers and non-relapsers) reported no drinking since the last EMA assessment.

Third, we examined the association between relapse status and EMA variables. Relapse Status (Relapsers vs. Non-relapsers) and Assessment Type (TA vs. RA) were included in all models. Given that it was expected that study measures would be significantly different during TAs (vs. RAs), and given that relapse risk might arguably be best assessed from responses in TAs (Marhe et al., 2013) we tested the interaction term between Relapse Status and Assessment Type. If a significant interaction was not observed, the interaction term was dropped from the model and the F value for Relapse Status from the reduced model was reported.

Last, the aforementioned analyses used data from all assessments. We also performed the same analyses but excluding those assessments from relapsers completed after their first reported relapse. These analyses examined whether relapsers who provided EMA data prior to relapse ($n=7$) and non-relapsers ($n=31$) differed on EMA variables prior to relapse.

Results

Descriptive Statistics

We first compared the EMA participants ($n=43$) with the participants of the parent study who did not participate in the EMA protocol ($n=16$) (Table 1). There were no significant differences on age, gender, educational level, number of dependence symptoms, and use of medication (all p 's > .09).

All participants provided at least one week of EMA data, and 39 (90.7%) completed all 4 weeks of data collection. Overall, the 43 participants completed 2020 assessments (1870 RAs; 150 TAs). Participants completed on average 77.0% of RAs that were presented.

Table 1. Demographic characteristics of EMA and non-EMA participants of the parent study

	EMA participants (<i>n</i> = 43)		Non-EMA participants (<i>n</i> = 16)		<i>t</i> / χ^2	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Age	48.5	10.8	46.9	10.0	- 0.49	.63
Proportion men (in %)	69.8	-	81.3	-	0.78	.38
Educational level (in %)					2.76	.60
<i>High school</i>	25.6	-	18.8	-		
<i>Vocational education</i>	25.6	-	43.8	-		
<i>Higher vocational education</i>	27.9	-	12.5	-		
<i>University</i>	16.3	-	18.8	-		
<i>Other</i>	4.7	-	6.3	-		
Proportion medication users (in %)	62.8	-	50.0	-	0.79	.37
Number of dependence symptoms	8.21	2.13	7.13	0.52	1.74	.09
Number of previous treatments	1.40	1.89	0.69	0.60	1.46	.15

Relapse

Overall, 12 participants were designated as “relapsers” and 31 as “non-relapsers”. This latter group included two “controlled” drinkers and two “occasional” drinkers, who reported drinking during EMA but did not meet criteria for a relapse. Of the 12 relapsers, 5 reported having relapsed at the

first laboratory visit (i.e. before initiating the EMA protocol), and 7 completed at least one EMA assessment before relapse. The mean days to relapse for these seven participants was 8.14 (SD=6.44, Range 1–19 days). Overall relapsers completed 485 assessments (54 TAs, 431 RAs), 82 of which were completed prior to relapse (7 TAs, 75 RAs). Relapsers and non-relapsers did not differ in gender (33.33% and 29.03% females respectively, $\chi^2(1)=0.08$, $p=.78$) or use of medication (33.33% and 38.71% medication users respectively, $\chi^2(1)=0.11$, $p=.74$).

Natural History of Temptations

On average participants completed 43.5 (SD=20.0) RAs and 3.49 (SD=4.66) TAs. Thirty five participants (81.4%) completed at least 1 TA; these participants completed an average of 4.29 (SD=4.82, Range 1-21) TAs.

Figure 2 reports the mean number of TAs per study day by relapse group. There was no difference in number of TAs between relapsers and non-relapsers, $F(1,880)=0.58$, $p=.45$, but over both groups, the number of reported TAs per day declined over time, $F(1,880)=19.03$, $p<.0001$. Figure 2 also reports mean craving ratings over time by relapse group. Relapsers reported higher craving ratings than non-relapsers, $F(1,1933)=20.08$, $p<.0001$, and the same was true for Tempted Now and Tempted Past Hour (p 's < .0001).

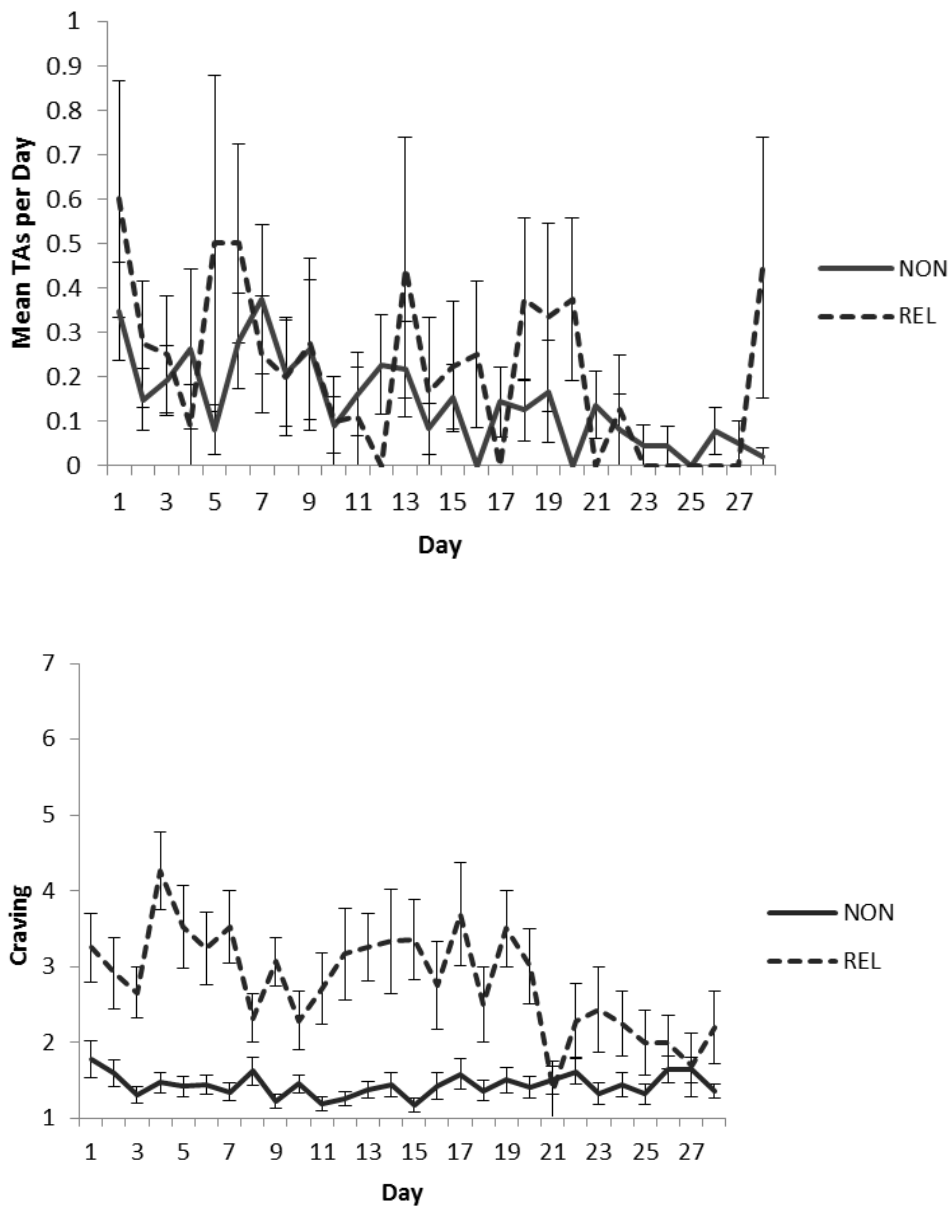


Figure 2. Mean number of TAs and mean craving ratings

Comparison of TAs and RAs in Whole Sample

Summary statistics are presented in Table 2 and results of LMMs in Table 3. Over all participants and assessments, participants reported higher ratings at TAs vs. RAs on Tempted Now, Tempted Past Hour, Craving, Negative Affect, Stress Now, and Stress Past Hour. Participants reported lower ratings on Abstinence Motivation at TAs vs. RAs. Ratings of Positive Affect did not differ between RAs and TAs.

Table 2: Summary Statistics

Measure ↓	Whole sample (N=43)		Relapsers (n=12)		Relapsers - Assessments Before Relapse (n=7)		Non-relapsers (n=31)	
	RAs	TAs	RAs	TAs	RAs	TAs	RAs	TAs
	n=1870	n=150	n=431	n=54	n=75	n=7	n=1439	n=96
<i>Tempted Now</i>	1.71 (1.42)	2.55 (2.16)	2.74 (1.99)	3.76 (2.32)	1.95 (1.20)	3.00 (2.16)	1.40 (1.01)	1.86 (1.73)
<i>Tempted Past Hour</i>	1.73 (1.43)	2.45 (2.11)	2.84 (2.00)	3.67 (2.31)	2.05 (1.32)	3.14 (2.19)	1.39 (0.99)	1.77 (1.64)
<i>Craving</i>	1.72 (1.41) ^a	2.54 (2.14)	2.76 (1.98)	3.81 (2.23)	2.07 (1.35)	3.57 (1.99)	1.40 (1.01) ^d	1.82 (1.72)
<i>Positive Affect</i>	3.25 (0.86) ^a	3.14 (0.86)	3.04 (0.87)	3.28 (0.88)	3.19 (0.68)	3.40 (0.42)	3.31 (0.84) ^d	3.06 (0.84)
<i>Negative Affect</i>	1.39 (0.63) ^a	1.62 (1.00)	1.47 (0.58)	1.99 (1.14)	1.23 (0.38)	2.14 (0.85)	1.36 (0.64) ^d	1.41 (0.85)
<i>Stress Now</i>	1.49 (0.81) ^a	1.78 (1.16) ^b	1.63 (0.86)	2.34 (1.19) ^c	1.48 (0.70)	2.43 (0.98)	1.45 (0.79) ^d	1.48 (1.03)
<i>Stress Past Hour</i>	1.46 (0.80) ^a	1.78 (1.16) ^b	1.54 (0.78)	2.32 (1.28) ^c	1.43 (0.64)	2.00 (1.15)	1.44 (0.78) ^d	1.48 (0.98)
<i>Motivation</i>	6.34 (1.34) ^a	5.95 (1.75) ^b	5.10 (2.05)	4.79 (2.15) ^c	6.08 (0.96)	6.57 (0.79)	6.72 (0.68) ^d	6.59 (1.04)

Note: Data are Mean (1 S.D.) aggregated over all pertinent assessments. ^a n=1869; ^b n=149; ^c n=53; ^d n=1438

Table 3: Results of LMMs for Whole Sample (N=43), Relapsers (n=12), and Non-relapsers (n=31)

Item/Measure ↓	Whole Sample (N=43)					Relapsers (n=12)					Non-relapsers (n=31)				
	<i>df</i>	<i>PE</i>	<i>SE</i>	<i>F</i>	<i>p</i>	<i>df</i>	<i>PE</i>	<i>SE</i>	<i>F</i>	<i>p</i>	<i>df</i>	<i>PE</i>	<i>SE</i>	<i>F</i>	<i>p</i>
<i>Tempted Now</i>	1, 34	0.98	0.24	17.03	.0002	1,10	1.19	0.42	7.81	.02	1,23	0.79	0.27	8.5	.008
<i>Tempted Past Hour</i>	1, 34	0.75	0.22	11.86	.002	1,10	0.82	0.39	4.58	.058	1,23	0.63	0.26	5.93	.02
<i>Craving</i>	1, 34	0.84	0.23	13.07	.001	1,10	1.04	0.43	5.95	.03	1,23	0.64	0.27	5.65	.03
<i>Positive Affect</i>	1, 34	-0.09	0.07	1.73	.20	1,10	0.06	0.12	0.23	.64	1,23	-0.19	0.09	4.15	.053
<i>Negative Affect</i>	1, 34	0.35	0.10	11.50	.002	1,10	0.70	0.20	11.72	.007	1,23	0.19	0.11	3.25	.08
<i>Stress Now</i>	1, 34	0.39	0.14	8.16	.007	1,10	0.81	0.19	18.83	.002	1,23	0.15	0.15	0.99	.33
<i>Stress Past Hour</i>	1, 34	0.40	0.14	8.29	.007	1,10	0.87	0.23	14.61	.003	1,23	0.17	0.14	1.44	.24
<i>Motivation</i>	1, 34	-0.47	0.16	8.55	.006	1,10	-0.94	0.36	6.66	.03	1,23	-0.22	0.14	2.46	.13

Note: Data are parameter estimates for the effect of Assessment type on study measures (see text for details), *PE* = (unstandardized) parameter estimate; *SE* = standard error; *F* = *F* value from LMM

We conducted supplementary analyses omitting all assessments at which drinking was reported, leaving 1685 RAs and 126 TAs. LMMs revealed that Tempted Now, Tempted Past Hour, and Craving (all p 's < .01), as well as Negative Affect ($PE=0.26$, $SE=0.10$, $p=.02$) were higher at TAs than at RAs. Stressed Now ($PE=0.29$, $SE=0.13$, $p=.04$), and Stressed Past Hour ($PE=0.32$, $SE=0.14$, $p=.03$), were elevated during TAs while Positive Affect ($PE=-0.20$, $SE=0.08$, $p=.02$), and Abstinence Motivation ($PE=-0.40$, $SE=0.18$, $p=.03$) were lower during TAs. These analyses confirm that an effect of assessment type is present at times when participants reported no recent drinking.

Comparison of TAs and RAs by Relapse Group

Regarding negative affect and stress, one possibility is that, compared to non-relapsers, relapsers are more likely to experience and report temptations when experiencing stress and negative affect. Alternatively, the experience of temptations may be more negative affect-inducing for relapsers than non-relapsers. In general, the effect of assessment type tended to be larger in relapsers (Table 2-3). The Relapse Group x Assessment Type interaction was significant for Negative Affect, $F(1,1939)=5.42$, $p=.02$, Stress Now, $F(1,1939)=7.57$, $p=.006$, Stress Past Hour, $F(1,1939)=7.12$, $p=.008$, and Motivation, $F(1,1939)=4.11$, $p=.04$. The interaction was not significant for Positive Affect, Temptation Now, Temptation Past Hour, and Craving (all p 's > .09). In the reduced model (without the interaction term) there was a main effect for Relapse Group for Temptation Now, Temptation Past Hour, and Craving (all p 's < .0001), confirming that, averaged across TAs and RAs, relapsers reported higher temptation and craving ratings than non-relapsers.

Comparison of TAs and RAs Prior to Relapse

Table 2 also reports data excluding assessments that occurred after the first relapse. The Relapse Group x Assessment type interaction did not reach significance for any variable (all p 's > .08). In the reduced model (without the interaction term) there was a main effect of Relapse Group for Temptation Past Hour, $F(1,1550)=5.07$, $p=.02$, and Abstinence Motivation, $F(1,1549)=8.01$, $p=.005$, indicating that overall, relapsers (vs. non-relapsers) had higher temptation ratings and lower abstinence motivation while abstinent.

Discussion

This study investigated the natural history of temptation episodes in alcohol-dependent outpatients. The main findings were as follows. First, participants reported on average 3.5 temptations during the 4-week study period, and the majority (81%) reported at least one temptation. Relapsers did not report more temptations than non-relapsers but they did report higher craving over the study period. Second, participants reported higher levels of craving, negative affect and stress, and lower levels of abstinence motivation, at TAs than at RAs. Third, the effects of assessment type (TAs vs. RAs) were generally larger in relapsers than in non-relapsers. Last, before relapse had occurred the subsequent relapsers reported generally higher temptation ratings and lower motivation ratings than non-relapsers.

The frequency of temptation episodes in our sample was comparable to the frequency of alcohol craving reported by several studies in alcohol-dependent samples (Cooney et al., 2007; Krahn, Bohn, Henk, Grossman, & Gosnell, 2005; Litt et al., 2000; Tiffany, 1990). Additionally, craving ratings at TAs were comparable to craving ratings at TAs in a heroin-dependent sample (Marhe et al., 2013), while craving ratings of the non-relapsers were comparable to those reported by abstinent alcohol-dependent patients (Litt et al., 1998), indicating that craving is an important symptom that needs to be monitored during and after treatment.

Overall, participants reported higher levels of stress and negative affect at TAs than at RAs. These results are in line with data from other EMA studies involving heroin-dependent and cocaine-dependent patients (Epstein et al., 2009; Marhe et al., 2013; Preston & Epstein, 2011). Because negative affect was assessed during TAs, we cannot infer if negative affect preceded the TA, or whether the onset of a TA preceded the negative affect. For example, it may be that negative affect was already higher before the temptation episode and aided in precipitating a TA, as suggested by the Affective Processing Model of Negative Reinforcement (Baker et al., 2004). This model states that the accumulation of negative affect can result in craving (and presumably a temptation). Alternatively, the experience of a temptation episode may rapidly result in higher levels of negative affect (Schlauch, Gwynn-Shapiro, Stasiewicz, Molnar, & Lang, 2013). Finally, TAs and elevated negative affect may be unrelated, and caused by a third, unseen, variable (spurious relationship).

In common with other studies, frequency of temptation episodes was not associated with relapse (Marhe et al., 2013). However, relapsers

reported higher overall craving ratings than non-relapsers. In addition, relapsers reported greater increases in negative affect and stress, and greater decreases in abstinence motivation at TAs (vs. RAs). Individuals who report generally higher craving ratings, and individuals who report large increases in negative affect and stress at TAs (vs. RAs), and larger drops of abstinence motivation at TAs (vs. RAs), could be at risk for poor outcomes. Regarding negative affect and stress, one possibility is that relapsers, compared to non-relapsers, are more likely to experience and report temptations when experiencing stress and negative affect. Alternatively, the experience of temptations may be more negative affect-inducing for relapsers than non-relapsers.

Abstinence motivation was already lower in the relapsers before their first relapse. However, the number of available assessments prior to relapse was small. These results should be treated with caution pending replication. It is important to further study the conditions under which abstinence motivation becomes weaker, since lower abstinence motivation could be a risk factor for experiencing temptations or for relapse.

The study had a number of strengths. First, we were able to describe the natural history of temptation episodes and craving in alcohol-dependent patients over a 4-week period which, to our knowledge, has not been done using electronic devices. Second, we obtained a relatively large number of TAs, which bolsters confidence in our analyses of assessment type, and which provides new information about the real-world experiences of alcohol-dependent patients trying to maintain abstinence.

The study also had limitations. First, the number of relapsers was relatively small ($n=12$), meaning that our findings regarding relapse should be replicated in a larger sample. In particular, because the relapsers generally relapsed early, the majority of assessments from relapsers occurred after relapse. Thus, there is uncertainty as to whether the observed differences between relapsers and non-relapsers are a cause or consequence of relapse. Third, and relatedly, there were a relatively few number of relapsers with assessments that occurred prior to relapse ($n=7$), which meant that there was low power to detect interactions in analyses of assessments occurring during abstinence. Last, as noted earlier, we cannot make causal inferences about the direction of observed relationships.

In future studies, it is necessary to investigate the temporal relationships between negative affect, stress, abstinence motivation, and temptation episodes/craving in larger samples. Knowledge of whether

negative affect precedes or follows temptation episodes may be useful for treatment. For example, if negative affect precipitates temptations then emotion regulation training could potentially reduce the occurrence of temptation episodes. If temptation episodes and/or craving provoke negative affect, anti-craving medication may potentially reduce the occurrence of negative affect.

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Chapter 7: General discussion

General Discussion

This thesis focuses on determinants of relapse and craving in individuals with alcohol dependence. Both relapse and craving are important characteristics of alcohol dependence and therefore it is important to explore determinants of both phenomena in greater detail. The importance of mapping determinants of relapse lies in the fact that still many patients who have reached abstinence eventually relapse. Often reported determinants of relapse include craving (Franken, 2003; Higley et al., 2011), negative affect (Baker et al., 2004; Sinha et al., 2009; Walitzer & Dearing, 2006; Witkiewitz & Villarroel, 2009), implicit processes (Tiffany, 1990; Wiers & Stacy, 2006), and sensitivity for alcohol-related cues (Carter & Tiffany, 1999; Grüsser et al., 2004; Robinson & Berridge, 1993, 2001; Tapert et al., 2003). Additionally, even though there is still debate on the role of craving in relapse (e.g., Holt, Litt, & Cooney, 2012) craving has been added to the list of diagnostic symptoms for alcohol dependence in the DSM-5 (American Psychiatric Association, 2013) stressing the importance of mapping the determinants of craving in further detail.

Therefore, the overall aim of this thesis was to explore proximal determinants of relapse and craving in abstinent alcohol-dependent outpatients.

The following research questions were addressed in this thesis:

1. What do alcohol-dependent patients themselves report as being determinants of relapse and of craving?
2. Is sensitivity for alcohol-related cues enhanced by stress?
3. Are attentional bias and approach/avoidance tendencies predictors of relapse in alcohol-dependent outpatients?
4. Are trait anxiety and drinking motives related to craving?
5. Do stress, negative affect and abstinence motivation change when patients experience temptation episodes?

Four studies, reported in five Chapters, were performed to answer the research questions. In this Chapter the main findings of these studies will be described first. Second, the study findings are integrated and discussed in relation to the overall aim of this thesis. Third, methodological issues are discussed that should be taken into consideration when interpreting the findings. After that, the implications for practice of the integrated findings are

discussed. Finally, directions for future research are given based on the overall conclusions of this thesis.

Main findings

In Chapter 2 determinants of relapse and of craving were explored by conducting semi-structured interviews with alcohol-dependent patients. Patients were asked about the main reasons for their most recent relapse. In addition, patients reported on the determinants of craving episodes which did not result in a relapse. Relapse determinants that were reported most often were negative affect and testing personal control (i.e., opting for controlled drinking, which escalated into drinking at pretreatment drinking levels). Craving was not often reported as being a determinant of relapse according to the patients. Relapses were preceded by multiple determinants, whereas craving was preceded by only one determinant. Additionally, craving was most often preceded by negative affect and alcohol-related cues according to patients. These results show that negative affect seems to play an important role, both in instigating a relapse and in evoking craving in alcohol-dependent outpatients.

Chapter 3 reports on the association between stress and sensitivity for alcohol-related cues. This association was investigated through a literature review. Studies were included in the review if they concerned studies on alcohol users and included a stress induction and a measure of cue sensitivity (i.e., assessment of craving, physiological measures, or a measure of attentional bias). The study shows that there is a relationship between stress and alcohol cue sensitivity: higher stress levels were accompanied by higher levels of cue sensitivity. This effect was most pronounced in individuals with comorbid PTSD and in participants who drink to cope with negative affect. These results suggest that stress affects cue sensitivity in populations that already experience more negative affect due to either psychiatric comorbidity or a habit of drinking in stressful situations.

Chapter 4 tested whether attentional bias and approach/avoidance tendencies were predictive of relapse within three months after assessment of these processes. We tested the hypothesis that attentional bias and approach/avoidance tendencies are predictive of relapse by assessing both processes at the beginning of treatment and again four weeks later. Our patients showed an attentional bias for alcohol-related cues. In addition, they

displayed the tendency to avoid alcohol-related stimuli. However, both implicit processes were not predictive of relapse, indicating that implicit processes are a characteristic of alcohol dependence but they do not have predictive value for relapse. Additionally, our results indicate that attentional bias and avoidance tendencies were not stable over time reducing the possibility of using these processes for long-term prediction over time.

Chapter 5 explored whether coping motives to drink moderated the relationship between trait anxiety and craving during treatment. The relationship between trait anxiety and craving had been well established in previous research, but the role of coping motives in this relationship had not yet been investigated. In addition, the moderating role of coping motives was also explored in the relationship between trait anxiety and pretreatment alcohol consumption. Whereas we did find evidence for the moderating role of coping motives in the relationship between trait anxiety and craving during treatment, we did not find evidence for a relationship between trait anxiety, coping motives, and pretreatment alcohol consumption. The interplay between trait anxiety and coping motives was related to intensified craving, not to pretreatment drinking levels.

In Chapter 6, we investigated the natural history of temptation episodes using Ecological Momentary Assessment techniques. Together with monitoring frequencies of temptation episodes, we assessed levels of stress, craving, abstinence motivation and negative and positive affect during these episodes and at random times throughout the day. Temptation episodes were not very frequent, but these episodes were accompanied by higher levels of stress, craving and negative affect, and by lower levels of abstinence motivation. When distinguishing between alcohol-dependent outpatients who did relapse and those who did not relapse during the study, we found that the patients who relapsed during the study had stronger temptation episodes than the patients who did not relapse. These results suggest that the intensity of temptation episodes may serve as an indicator of higher relapse risk.

Integration and reflection on main findings

In this section, the main findings of the studies presented in this thesis are discussed. First, the results on determinants of relapse will be discussed. Second, the results on determinants of craving will be reviewed.

Finally, an overall conclusion on determinants of relapse and craving is provided.

Determinants of relapse

We were able to bolster the hypothesis that negative affect is an important determinant of relapse. In Chapter 3, negative affect was the most reported determinant of a relapse by alcohol-dependent outpatients. In addition, in Chapter 6, higher levels of negative affect during temptation episodes were related to the relapse status of the patients: the patients who relapsed during the study, had higher levels of negative affect during temptation episodes than those patients who remained abstinent. Our results are in line with the Affective Processing model of Negative Reinforcement (Baker et al., 2004), which states that negative emotional states are predictive of relapse.

In addition, we found that stress enhances sensitivity for alcohol-related cues mainly in those individuals who consume alcohol to relieve negative affect (Chapter 3), and that alcohol-related stimuli were not one of the main self-reported determinants of relapse (Chapter 2). Based on the results from this thesis it seems that only under specific circumstances cue sensitivity, indicated by craving or attentional bias for alcohol-related cues, is a determinant of relapse. Our results point toward the presence of stress, or in the broader sense negative affect, combined with other determinants which leads to a relapse. The mere presence of cue sensitivity does not appear to be a risk factor for relapse.

Regarding the predictive value of implicit processes, we found that attentional bias and avoidance tendencies were not predictive of relapse (Chapter 4). This finding was against our expectations because previous research has shown that attentional bias (Cox et al., 2002; Marissen et al., 2006; Waters et al., 2003) and avoidance tendencies (Spruyt et al., 2013) were predictive of relapse. On the other hand, considering a recent review on the clinical utility of attentional bias as predictor of relapse (Christiansen, Schoenmakers, & Field, 2015), it seems that attentional bias for alcohol-related stimuli, and probably avoidance tendencies as well, may only be a characteristic of alcohol dependence. The review by Christiansen et al. (2015) showed that although attentional bias is often present in alcohol-dependent patients, it is not predictive of relapse. In contrast to Christiansen et al. (2015), there is evidence that an attentional bias toward drugs increases just before a relapse in a heroin-dependent inpatient sample (Marhe et al., 2013), indicating that attentional bias may be a more proximal

than a distal predictor of relapse, as was suggested by Field and colleagues (2014).

The results on avoidance tendencies (Chapter 4) showed that avoidance tendencies are present in alcohol-dependent outpatients trying to maintain abstinence, which is in line with other studies on approach/avoidance tendencies in alcohol-dependent patients (Spruyt et al., 2013). However, these results contrast with avoidance training studies, in which alcohol-dependent patients are trained to move away from alcohol-related stimuli (Eberl et al., 2013, 2014; Wiers et al., 2011). These training studies showed that training patients to avoid alcohol-related stimuli resulted in reduced relapse rates. Based on the current literature and the results from this thesis, the role of attentional bias and avoidance tendencies in predicting relapse is still unclear. Possibly, implicit processes play a role in relapse in the hours preceding the relapse but not in the longer period preceding the relapse. More research is needed to be able to draw firm conclusions.

The studies in this thesis show that the process leading to a relapse is dynamic and complex and trying to predict who relapses and who does not, is hard to do based on single predictors. Additionally, craving by itself was not an often reported determinant of relapses, which is also in line with previous research stating that craving does not always produce or precede a relapse (Drummond, 2001; Higley et al., 2011; Miller et al., 1996), and more determinants are needed to instigate a relapse, making relapse a complex process (Chapter 2). However, patients who do relapse, seem to have stronger cravings which are paired with higher levels of stress and negative affect, and lower levels of abstinence motivation (Chapter 6). Thus, it could be that alcohol-dependent individuals who experience stronger episodes of craving that are accompanied by stress and negative affect have a greater risk of relapsing than those individuals who do experience craving but have lower levels of stress and negative affect accompanying their craving. The results from the studies in this thesis show that the process leading to a relapse is complex, even when only examining proximal predictors.

Determinants of craving

In line with earlier studies (Glöckner-Rist et al., 2013; Oslin et al., 2009; Tiffany, 1990), we found that craving is infrequently reported by alcohol-dependent outpatients. Even though alcohol-dependent patients infrequently experience craving, negative emotional states and external

alcohol-related stimuli (e.g. passing a bar or seeing a liquor store) were reported as being the most frequent determinants when craving did occur (Chapter 2). In addition, in Chapter 3 we saw that psychological stress elevates cue sensitivity, often measured as degree of craving, mainly in those who drink to cope with negative affect. Those coping drinkers are at risk of stronger craving when they are also high in trait anxiety (Chapter 5; Litt, Cooney, & Morse, 2000).

Taken together, negative affect, endorsement of coping motives, and the presence of alcohol-related stimuli are important determinants of craving.

Integration of findings

Based on our results, negative affect is an important predictor of both relapse and craving. We have measured negative affect in various ways by measuring stress, trait anxiety and composite scores of negative affect. Stress and trait anxiety are predictive of craving, especially when an alcohol dependent individual is or was used to consume alcohol to cope with this negative affect. Coping motives to drink seems to serve as a vulnerability for the experience of craving. We also showed that craving is accompanied by higher levels of stress and negative affect in those individuals who had relapsed, but craving as a single predictor did not seem to be an important determinant of relapse. From our results we can conclude that the mere experience of craving is not a risk factor for relapse.

In addition, predicting relapse based on the measurement of attentional bias and approach/avoidance bias during treatment does not seem warranted. These biases were present in alcohol-dependent outpatients, but did not predict relapses within three months. Cue sensitivity, operationalized as attentional bias, does evoke craving especially in those who drink to cope with negative affect. In the same line, the presence of alcohol-related stimuli often provokes craving. Because attentional bias is a more unconscious process, it is hard for individuals to detect that they have an attentional bias, in this case for alcohol-related stimuli. Therefore, the presence of alcohol-related stimuli may serve as a proxy for attentional bias, indicating that attentional bias might be a predictor of craving, but not a predictor of relapse within three months after assessing attentional bias.

The finding that negative affect is an important predictor of relapse is in line with the Affective Processing Model of Negative Reinforcement (Baker et al., 2004). This model states that when stressors or abstinence causes

negative affect to grow, increasing negative affect interferes with information processing in ways that promote renewed alcohol consumption. In this model, negative affect is dealt with by consuming alcohol, a reaction that has developed by repeatedly consuming alcohol when confronted with negative affective states. When abstinent, experiencing negative affect will evoke craving or a relapse.

When looking at the frequency of craving episodes, we found that alcohol-dependent patients infrequently experience craving episodes. However, there are great individual differences in the frequency and intensity of craving, and stronger craving episodes seem to occur in those who relapse compared to those who do not relapse.

Methodological considerations

In this section the strengths and limitations of the studies in this thesis are being discussed.

Strengths

The strength of this thesis lies in the fact that multiple research methodologies were used to explore determinants of relapse and of craving. Studying the same phenomenon using different methodologies makes it possible to cross-check data from multiple sources to search for regularities in the data. In this thesis, we explored the determinants of relapse and of craving using different methodologies: interviews, observational data, literature review, and EMA methodology.

Another strength of this thesis is that, except for Chapter 3 which also included heavy and social drinkers, alcohol-dependent outpatients were under investigation. This is a challenging population to include in research, but we succeeded to keep the majority of participants in the studies even if participants had relapsed or even terminated their treatment prematurely. Keeping participants motivated for this research and providing a non-judgmental atmosphere aided in continuing participation, according to participants.

Additional strength of this thesis is that EMA methodologies were used to provide information on the natural history of craving. To our knowledge, we are the first to explore the natural history of craving episodes in alcohol-dependent individuals using this methodology. In addition, we have showed that EMA methodology is feasible in an alcohol-dependent

sample. There were few drop-outs and the majority of our sample completed the full four-week protocol.

Limitations

When interpreting the results from the studies in this thesis, some limitations need to be taken into account. First, overall study samples were small. Small samples do not have enough power to detect small effect sizes. On the other hand, investigating determinants of behavior to try and predict this behavior is better served with finding large effects. If effect sizes are large, determinants are of more use to the population under investigation, in this case alcohol-dependent outpatients. In this thesis, no large effect sizes were found, indicating that even though we utilized small samples and possibly missed small effect sizes, these small effects would not be relevant enough to develop an appropriate intervention for the larger population of alcohol-dependent outpatients.

Because our study's aim was to find clinical relevant effects, rather than merely theoretically interesting differences, clinical relevance would have been demonstrated when effect sizes had been bigger, making it possible to predict relapse on an individual level, or at the very least on very small subsets of patients. In Chapter 2, we investigated self-reported determinants of relapse and of craving in a small sample of 20 patients. In qualitative research, saturation is an often employed criterion to stop including participants in the study. In this thesis, saturation was reached after approximately 16 interviews, bolstering our confidence that we obtained a representative overview of determinants of craving and of relapse.

EMA methodology, even though it has its strengths, also has its limitations. For example, we cannot be certain that the temptation assessments that were started by patients themselves are all actual temptation episodes. When using EMA methods, there is always a chance that participants inappropriately use the self-initiated assessments, in this case TAs, to compensate for missed random assessments. In Chapter 6, we did not check whether this was the case. However, since at TAs mean craving and temptation ratings were higher than at RAs, we may assume that the TAs were indeed initiated when patients were having a temptation episode. Another related point is that we cannot infer if a TA was initiated at the beginning of a temptation episode or that the episode was already ongoing when the assessment was started. We therefore also cannot infer how long a temptation episode lasts. Another limitation of the design of our EMA study is that it was not possible to draw causal inferences based on our

data. All measures in the EMA study were obtained simultaneously and there was not enough data to investigate the causal pathways between stress, abstinence motivation, negative affect, and the experience of craving.

Overall, a main limitation of this thesis is that only proximal determinants of relapse and of craving were under investigation. It is possible that more distal predictors also played a role in evoking a relapse or craving. As stated in the dynamic model of relapse, background factors provide the basis for the general risk for relapse an individual has (Witkiewitz & Marlatt, 2004). Because we did not measure these more distal factors, we cannot infer what their influence was on the relapses our participants experienced.

Data from studies in this thesis, except for Chapter 4, were all cross-sectional in nature. Cross-sectional data allows for finding associations between variables, but not for finding causal relations.

Implications for practice

The results from the studies in this thesis point toward a personalized approach during treatment concerning developing coping skills to deal with temptation episodes. Those patients who are predisposed to experience negative affect more often and consumed alcohol to cope with this negative affect before initiating treatment experienced stronger cravings during treatment (Chapter 5). Additionally, patients who relapsed had temptation episodes characterized by stronger craving and negative affect than those who did not relapse (Chapter 6). Therefore, these patients should be provided with more tools to learn to deal with cravings accompanied by stronger negative affect and lower abstinence motivation without starting to drink again.

Recently, research on treatment for alcohol dependence has been focusing on mindfulness as a promising addition to current treatment strategies (Crescentini, Matiz, & Fabbro, 2015; Murphy & MacKillop, 2014; Waters, Reitzel, et al., 2009). Mindfulness is defined as a receptive attention to and awareness of present events and experiences without acting on those events and experiences (Brown & Ryan, 2003). In the case of alcohol dependence mindfulness reflects the perception of environmental cues and internal states without acting on them by drinking (Bowen et al., 2014). This would imply that when alcohol-dependent patients learn mindfulness skills, they would not act when experiencing negative affect, the main determinant of relapse and craving in this thesis, making it less likely that patients would relapse.

Another recent development is the interest in designing and implementing mobile health applications (MHapps). Currently, one of the MHapps that has been developed and tested in alcohol-dependent patients shows promising results (Gustafson et al., 2014). This app is designed to provide effective continued care after residential treatment and for example contains a panic button, GPS-signaling for high risk locations, and weekly check-ins. The first results showed that patients who used the app had less risky drinking days in the twelve months following treatment than those who did not use the app (Gustafson et al., 2014). One advantage of such apps is that it can be used real-time, providing support as needed. As stated in Chapter 2, relapse is often the result of the occurrence of multiple determinants which accumulate in everyday life. An MHapp could assist when patients feel that they are at the brink of drinking and need or want help from their counselor to help them overcome the risky situation.

Directions for future research

In this section, directions for future research are given, based on the results obtained in this thesis. First, this thesis only focused on proximal predictors of relapse. When looking at the dynamic model of relapse (Witkiewitz & Marlatt, 2004) relapse is evoked by a dynamic interplay of distal and proximal determinants. The studies in this thesis did examine proximal determinants of relapse, such as negative affect and implicit processes; future research would benefit from incorporating more distal predictors such as family history and dependence severity, allowing for a better test of the dynamic model of relapse.

The role of coping motives should be investigated further since we found evidence in this thesis for a moderating role of coping motives in two relationships: in the relationship between trait anxiety and craving and in the relationship between stress and alcohol cue sensitivity. There is still little research on coping motives in samples of dependent patients. Because in our studies we found evidence for the moderating role of coping motives in the relationship between negative affect and craving, we believe that future studies should take into account coping motives to drink, to further study the effect of these coping motives on evoking craving.

In recent years, EMA studies have been conducted using mobile phones, either participants' own mobile phone or one provided by the investigators (e.g. Brodbeck, Bachmann, Brown, & Znoj, 2014; Schüz, Walters, Frandsen, Bower, & Ferguson, 2014; Thrul, Bühler, & Ferguson,

2015). One of the advantages of using mobile phones is that the use of these devices is very common these days, which will aid in study acceptance by participants (Clough & Casey, 2011). On the other hand, EMA studies using mobile phones have shown lower protocol compliance than studies using other electronic devices (Thrul et al., 2015). While promising, there is still room for improvement when using mobile phones for EMA research. Another idea is to track participants by combining GPS data with EMA methods. Epstein and colleagues have tested whether combining these two into Geographical Momentary Assessment (GMA) would be feasible in a challenging population of opioid-dependent polydrug users (Epstein et al., 2014).

EMA methodology also seems appropriate to further investigate the predictive properties of attentional bias and avoidance tendencies. As mentioned earlier, there is still much debate on the predictive properties of attentional bias (e.g., Christiansen et al., 2015). However, there is evidence that attentional bias is elevated in the hour before a temptation episode in heroin-dependent patients, indicating that attentional bias may be a proximal precursor of a temptation episode (Waters et al., 2012). Future research should further investigate whether attentional bias is elevated prior to a temptation episode or even a relapse. In addition, because we did find that avoidance tendencies predicted a relapse within three months of initiating treatment whereas other studies did (Spruyt et al., 2013), using EMA methodology could also be used to further investigate if and how avoidance tendencies contribute to the instigation of a temptation episode or a relapse.

Finally, we believe that using EMA methodology to further investigate relapse and craving in abstinent alcohol-dependent outpatients is a good way forward to fully explore the processes that lead to craving and to relapse. In addition, the more distal factors that may play a role in relapse, such as dependence severity and family history of dependence, should then also be taken into account, as suggested by the dynamic model of relapse (Witkiewitz & Marlatt, 2004)

Closing Remark

In sum, the results from this thesis have shown that the process leading to relapse is a complex one. In addition, this thesis showed that the mere presence of craving is not an important determinant of relapse. However, special attention should be directed toward the severity of craving in alcohol-dependent patients because stronger cravings accompanied by

higher levels of negative affect were associated with relapse. Therefore, we suggest that treatment for alcohol-dependence moves towards teaching patients how to lower craving levels when they encounter risky situations, thereby possibly reducing the risk for relapse in alcohol-dependent patients.

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Summary

Despite years of research and improvements in treatment and prevention, relapse in alcohol dependence remains a problem. Even though many patients become abstinent or controlled drinkers after treatment, relapse rates remain high. Therefore, the goal of this thesis was to explore determinants of relapse, focusing on those determinants that are present in the moments leading up to a relapse, so-called proximal determinants.

Using the dynamic model of relapse (Witkiewitz and Marlatt, 2004), proximal determinants of relapse were examined in this thesis. Especially the role of craving, negative affect, alcohol-related stimuli and implicit processes were subject of investigation. Additionally, since craving is often seen as important to relapse even though a firm empirical foundation is lacking, extra attention was given to craving and its determinants.

The above was operationalized by means of the following research questions:

1. What do alcohol-dependent patients themselves report as being determinants of relapse and of craving?
 2. Is sensitivity for alcohol-related cues enhanced by stress?
3. Are attentional bias and approach/avoidance tendencies predictors of relapse in alcohol- dependent outpatients?
 4. Are trait anxiety and drinking motives related to craving?
5. Do stress, negative affect and abstinence motivation change when patients experience temptation episodes?

Chapter 2 explores the determinants of craving and relapse in a sample of 20 abstinent alcohol- dependent patients by means of semi-structured interviews regarding their most recent relapse and craving episodes. These interviews were reviewed for their thematic content, and codes capturing the thematic content were formulated. Results showed that the

presence of alcohol-related stimuli and experiencing negative emotional states were often occurring determinants of craving, whereas testing personal control and negative emotional states were often reported determinants of relapse. Additionally, results revealed that relapse was preceded by multiple determinants while craving episodes were preceded by only a single determinant. Descriptions of craving episodes also revealed that these episodes tend to vary in intensity and frequency. Finally, in this sample of abstinent alcohol-dependent patients, craving by itself did not seem an important predictor of relapse.

In **Chapter 3** the literature concerning the influence of stress on the sensitivity for alcohol-related cues is being reviewed. Empirical studies indexed in PubMed, EMBASE, PsycINFO, and Web of Knowledge that assessed the relation between stress and sensitivity for alcohol-related cues using subjective, behavioral and/or physiological measures were included in the review. Of the 359 articles screened, 12 were included in the review. The literature shows that there is a relationship between stress and sensitivity for alcohol-related cues. Reviewed studies reported that higher stress levels were accompanied by higher levels of cue sensitivity and that this effect was most pronounced in individuals with comorbid PTSD and in participants who drink to cope with negative affect. It seems that stress affects cue sensitivity in those who already experience more negative affect due to either psychiatric comorbidity or a habit of drinking in stressful situations.

Chapter 4 tested whether attentional bias and approach/avoidance tendencies (i.e. implicit processes) were predictive of relapse in abstinent alcohol-dependent outpatients. Fifty abstinent alcohol-dependent patients completed the Addiction Stroop Task, which assesses attentional bias, and the Stimulus-Response Compatibility Task, which measures approach/avoidance tendencies. Time to relapse was assessed one, two, and three months after the bias assessment. In this study, patients showed an attentional bias in addition to a tendency to avoid alcohol-related stimuli. However, both implicit processes were not predictive of relapse within three months after assessing these processes. These findings imply that implicit processes are a characteristic of alcohol dependence but they do not have predictive value for relapse.

Chapter 5 explored whether the relationship between trait anxiety and craving was moderated by drinking to cope with negative affect. Additionally, the moderating role of coping motives in the relationship between trait anxiety and pretreatment alcohol consumption. Fifty-nine abstinent alcohol-dependent outpatients underwent measurements of drinking to cope with negative affect, craving, trait anxiety, and weekly alcohol consumption before treatment to examine the moderating role of coping motives in the relationship between anxiety, craving and alcohol consumption. The results showed that coping motives did moderate the relationship between trait anxiety and craving (e.g., in outpatients with high coping motives, trait anxiety predicted craving, but not in outpatients with low coping motives) but there was no evidence for a relationship between trait anxiety, coping motives and pretreatment drinking levels.

In **Chapter 6**, the natural history of temptation episodes was under investigation. Using Ecological Momentary Assessment (EMA) methodologies, not only the frequency and intensity of temptation episodes were investigated, but also levels of stress, craving, abstinence motivation, and negative and positive affect accompanying these episodes. Additionally, these factors were also assessed at random times during the day for four weeks. Using personal digital assistants (PDA's), participants were signaled to complete assessments three times a day (random assessments, RAs). They were also instructed to complete an assessment when they experienced craving for alcohol or came to the brink of drinking without doing so (temptation assessments, TAs). Assessments included current craving, current positive and negative affect, current and past-hour stress, and current motivation to remain abstinent. Temptation episodes were reported infrequently, but when reported these episodes were accompanied by higher levels of stress, craving and negative affect, and by lower levels of abstinence motivation. Patients that relapsed during the study had stronger temptation episodes than those who did not relapse. The results suggest that the intensity of temptation episodes may serve as an indicator of higher relapse risk.

Chapter 7 addresses the main findings, methodological considerations, and implications for practice and further research. Overall, negative affect, including stress, was an important predictor of both relapse and

craving. More specifically, negative affect is an important determinant of relapse but is accompanied by other determinants when a patient relapses. However, predicting relapse based on a prior measurement of attentional bias or avoidance tendencies during treatment does not seem warranted even though these biases seem to be present in abstinent alcohol-dependent outpatients.

When looking at determinants of craving, stress and anxiety are predictive of craving, and drinking to cope with negative affect seems to serve as a vulnerability for experiencing craving. Additionally, craving is accompanied by higher levels of stress and negative affect in those patients who had relapsed. However, patients infrequently experience craving and the intensity of episodes varies both between and within patients. Finally, the mere experience of craving was not a determinant for relapse.

In this thesis, only proximal determinants were examined. Future research would benefit from incorporating the more distal factors to get a more complete overview of the relapse process. Additionally, using EMA methodology to further investigate the relapse process in daily life to get an even more detailed insight into this process to aid in improving current treatments even further.

All results in this thesis point towards a personalized treatment approach concerning developing coping skills to deal with temptation episodes. Patients who experience more negative affect and also cope with negative affect by consuming alcohol seem to be predisposed to have stronger cravings. Patients who relapsed experienced stronger craving and negative affect during craving episodes. This implies that patients who experience stronger craving and negative affect should be provided with more tools for coping with negative affect when experiencing craving.

Samenvatting

Terugval bij alcoholverslaving blijft een probleem, ondanks jaren van onderzoek en doorgevoerde verbeteringen van behandelingen en preventie. Veel patiënten zijn abstinente of zijn gecontroleerde drinkers na hun behandeling maar toch vallen veel van deze patiënten terug in hun oude drinkpatroon. Om deze reden is het doel van dit proefschrift om determinanten van terugval in kaart te brengen waarbij is gefocust op determinanten die actief zijn vlak voordat een terugval plaatsvindt, de zogenoemde proximale determinanten.

Deze proximale determinanten zijn in kaart gebracht aan de hand van het dynamische terugvalmodel (Witkiewitz en Marlatt, 2004). De focus in dit proefschrift ligt voornamelijk op de rol van craving, negatief affect, alcoholgerelateerde stimuli en impliciete processen. Daarnaast is ook gelet op de determinanten van craving, aangezien craving vaak gezien wordt als een belangrijke determinant van terugval zonder dat daar een sterke empirische onderbouwing voor is.

Om de rol van bovenstaande proximale determinanten te onderzoeken, zijn de volgende onderzoeksvragen opgesteld:

1. Welke determinanten van terugval en craving worden door abstinente alcoholverslaafde patiënten gerapporteerd?
2. Wordt de gevoeligheid voor alcohol-gerelateerde stimuli versterkt door de aanwezigheid van stress?
3. Zijn aandachtsbias en approach/avoidance bias voorspellers van terugval bij ambulante alcoholverslaafde patiënten?
4. Is er een relatie tussen angstdispositie, drinkmotieven en craving?
5. Zijn er veranderingen in stress, negatief affect of motivatie om abstinente te blijven bij ambulante alcoholafhankelijke patiënten wanneer zij een episode van verleiding om te drinken ervaren?

In **Hoofdstuk 2** worden de determinanten van terugval en craving in kaart gebracht middels semigestructureerde interviews met abstinente alcoholverslaafde patiënten. Onderwerp van deze interviews was de meest recente terugval en de meest recente craving episodes. Aan de hand van de thematische inhoud zijn er codes opgesteld. Uit deze codering bleek dat de aanwezigheid van alcohol-gerelateerde stimuli en de ervaring van negatieve emoties vaak genoemd werden als determinant van de meest recente

terugval. Daarnaast bleek uit de resultaten dat er meerdere determinanten aanwezig zijn voorafgaand aan een terugval terwijl er slechts één determinant voorafging aan een craving episode. Uit de beschrijvingen van craving episodes bleek ook dat deze episodes verschillen qua intensiteit en frequentie. Tot slot bleek in deze steekproef van abstinente alcoholverslaafde patiënten dat craving op zich geen belangrijke determinant van een terugval is.

In **Hoofdstuk 3** wordt een overzicht gegeven van de literatuur over de invloed van stress op gevoeligheid voor alcohol-gerelateerde stimuli. Onderzoeken die de relatie tussen stress en gevoeligheid voor alcohol-gerelateerde stimuli hebben gemeten middels subjectieve, fysiologische en/of gedragsmaten zijn geïncorporeerd in het overzicht. Er is gebruik gemaakt van PubMed, EMBASE, PsycINFO en Web of Knowledge, dit leverde 359 artikelen op. Van deze artikelen zijn er 12 meegenomen in het literatuuroverzicht. Uit de literatuur bleek dat er een relatie is tussen stress en gevoeligheid voor alcoholgerelateerde stimuli. De onderzoeken lieten zien dat hogere stressniveaus samengaan met een verhoogde gevoeligheid voor alcohol-gerelateerde stimuli. Dit effect was het duidelijkst bij individuen met comorbide PTSS en bij individuen die drinken om te kunnen omgaan met negatief affect. Het lijkt dat stress een effect heeft op de gevoeligheid voor alcohol-gerelateerde stimuli, met name bij individuen die vanwege comorbiditeit of een gewoonte om te drinken tijdens stressvolle situaties.

In **hoofdstuk 4** wordt onderzocht of aandachtsbias en approach/avoidance bias een terugval voorspellen bij abstinente ambulante alcoholverslaafde patiënten. Aan vijftig abstinente alcoholverslaafde patiënten werden de Stroop-taak, welke aandachtsbias meet, en de Stimulus-Response Compatibility-taak voorgelegd, welke approach/avoidance bias meet. Één, twee en drie maanden na deze meting werd de tijd tot een terugval uitgevraagd bij de patiënten. Uit de resultaten bleek dat patiënten een aandachtsbias voor alcohol-gerelateerde stimuli vertonen en dat zij de neiging hebben alcohol-gerelateerde stimuli te vermijden. Beide biases bleken echter geen voorspeller van een terugval binnen drie maanden na het meten van deze biases. Deze resultaten impliceren dat impliciete processen een kenmerk van alcoholverslaving zijn maar dat zij geen voorspellende waarde hebben bij het voorspellen van een terugval bij alcoholverslaafde patiënten.

Hoofdstuk 5 onderzoekt de modererende rol van coping motieven om te drinken in de relatie tussen angstdispositie en craving tijdens de behandeling. Ook wordt de modererende rol van coping motieven in de relatie tussen angstdispositie en alcoholconsumptie voorafgaand aan de behandeling onderzocht. Bij 59 abstinente alcoholverslaafde patiënten werden de volgende variabelen gemeten: coping motieven, craving (tijdens behandeling), angstdispositie en alcoholconsumptie voorafgaand aan de behandeling. Uit de resultaten bleek dat coping motieven een modererende rol spelen in de relatie tussen angstdispositie en craving (bij patiënten die voornamelijk coping motieven gebruiken, werd craving voorspeld door de mate van angstdispositie maar niet bij patiënten die weinig gebruik maken van coping motieven). Er was echter geen bewijs voor een modererende rol van coping motieven in de relatie tussen angstdispositie en alcoholconsumptie voorafgaand aan de behandeling.

In **Hoofdstuk 6** werd het natuurlijk verloop van verleidingsepisodes in kaart gebracht. Om dit verloop in kaart te brengen is gebruik gemaakt van Ecological Momentary Assessment (EMA). Alcoholverslaafde patiënten kregen gedurende vier weken een personal digital assistant (PDA) mee. Deze PDA gaf drie keer per dag op willekeurige tijdstippen een signaal (random assessments, RAs), ook kregen patiënten de instructie om de PDA zelf te starten wanneer zij craving ervoeren of wanneer zij op het punt stonden weer te gaan drinken zonder dit daadwerkelijk te doen (verleiding, oftewel temptation assessments, TAs). Naast frequentie en duur van deze temptation episodes is bij RAs en TAs gevraagd naar de mate van stress, craving, negatief affect, positief affect en de motivatie voor abstinentie op dat moment. Verleidingsepisodes kwamen niet frequent voor, maar tijdens zo'n episode was er sprake van sterkere stress, craving en negatief affect, en van lagere motivatie tot abstinentie. Er was sprake van sterkere verleidingsepisode bij patiënten die tijdens het onderzoek een terugval hadden dan bij de patiënten die tijdens het onderzoek niet zijn teruggevallen. Deze resultaten suggereren dat de intensiteit van verleidingsepisodes een indicator is van een verhoogd risico op terugval.

In **Hoofdstuk 7** komen de belangrijkste bevindingen, een beschouwing van de gebruikte methodologie en implicaties voor de beroepspraktijk en vervolgonderzoek aan bod. In het algemeen was negatief affect, waaronder stress, een belangrijke voorspeller van terugval en craving. Hoewel negatief

affect als een belangrijke determinant wordt aangemerkt, gaat deze determinant wel samen met andere determinanten voordat een patiënt terugvalt. Terugval voorspellen op basis van aandachtsbias of avoidance bias lijkt niet mogelijk ondanks dat deze biases wel aanwezig zijn bij abstinente alcoholverslaafde patiënten.

Stress en angst blijken voorspellers van craving. Daarnaast lijken patiënten die coping motieven vertonen om te drinken, gevoeliger te zijn voor het ervaren van craving. Daarnaast gaat craving samen met het ervaren van meer stress en negatief affect bij patiënten die zijn teruggevallen. Patiënten ervaren craving echter niet frequent en ook de intensiteit van episodes varieert, zowel tussen patiënten als bij een patiënt zelf. Tot slot bleek dat het ervaren van craving op zich geen determinant van een terugval was. In dit proefschrift is alleen onderzoek gedaan naar proximale determinanten. Vervolgonderzoek zou zich naast deze determinanten ook moeten focussen op de meer distale factoren die een rol kunnen spelen bij een terugval om zo een completer beeld te krijgen van het totale terugvalproces bij alcoholverslaafde patiënten. Daarnaast zou het inzetten van EMA-methodologie een goede toevoeging zijn om een nog gedetailleerder beeld van het terugvalproces te verkrijgen en daarmee mogelijk huidige behandelingen verder te verbeteren.

Alle resultaten in dit proefschrift wijzen naar een gepersonaliseerde aanpak van de behandeling van alcoholverslaafde individuen. Binnen deze gepersonaliseerde aanpak zou er aandacht moeten zijn voor het aanleren van coping skills om te leren omgaan met verleidingsepisodes omdat is gebleken dat patiënten die veel negatief affect ervaren en hiermee hebben leren omgaan door alcohol te drinken, vatbaarder zijn voor het ervaren van sterkere craving. Daarnaast hadden de patiënten die terugvielen sterkere craving en negatief affect tijdens craving episodes. Dit wijst erop dat patiënten die sterkere craving en negatief affect ervaren, geholpen kunnen zijn met effectievere coping stijlen om te kunnen omgaan met negatief affect wanneer zij craving ervaren.

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Bij het IVO heb ik een geweldige tijd gehad, waar ik veel heb kunnen leren van mijn inmiddels oud-collega's. Cin, zonder jou geen IVO! Hulp bij alle administratieve klussen en altijd tijd voor een kop koffie en een luisterend oor. Lieve Alice, we zijn tegelijk gestart bij het IVO, in het souterrain weet je nog ;), ook jij bedankt voor de goede gesprekken met koffie, gezellige

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Curriculum Vitae

Michelle Snelleman was born on 5 april 1985 in Rozenburg, The Netherlands. In 2002 she completed secondary education at the Maerlant College, Brielle. Subsequently, she started studying Psychology at Leiden University where she obtained a Bachelor's degree in 2006. In 2010, she obtained a Master's degree in Psychology at the Erasmus University Rotterdam. After obtaining her Master's degree, she started the Academic Research Program at Erasmus University Rotterdam. In 2011, she started a PhD project on proximal determinants of relapse in alcohol dependence. This project was carried out by the IVO Addiction Research Institute. During her PhD project, she obtained a Master's degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES). From August 2015 she has been working as a research lecturer and study guidance counselor at Inholland University of Applied Sciences in Rotterdam.

Michelle Snelleman is geboren op 5 april 1985 in Rozenburg. In 2002 heeft zij haar middelbare schooldiploma behaald aan het Maerlant College te Brielle. Daarna is zij Psychologie gaan studeren aan de Universiteit Leiden, waar zij in 2006 haar Bachelorsdiploma heeft behaald. In 2010 behaalde zij haar Masterdiploma Psychologie aan de Erasmus Universiteit in Rotterdam waarna zij werd toegelaten tot het Advanced Research Program aan de Erasmus Universiteit in Rotterdam. In 2011 startte zij met haar promotietraject over de proximale determinanten van terugval bij patiënten met een alcoholverslaving. Dit project werd uitgevoerd door het IVO Instituut voor Onderzoek naar Leefwijzen en Verslaving. Tijdens haar promotietraject behaalde zij een Masterdiploma Clinical Epidemiology bij het Netherlands Institute for Health Sciences (NIHES). Vanaf augustus 2015 werkt zij als onderzoeksdocent en studieloopbaanbegeleider bij Hogeschool Inholland Rotterdam.

Academic publications

Peer-reviewed publications

- Bommel , J., Schoenmakers, T. M., Kleinjan, M., van Straaten, B., Wits, E., Snelleman, M., & van de Mheen, D. (2014). Perceived pros and cons of smoking and quitting in hard-core smokers: a focus group study. *BMC Public Health*, 14(1), 175. <http://doi.org/10.1186/1471-2458-14-175>
- Euser, A. S., van Meel, C. S., Snelleman, M., & Franken, I. H. a. (2011). Acute effects of alcohol on feedback processing and outcome evaluation during risky decision-making: an ERP study. *Psychopharmacology*, 217(1), 111–25. <http://doi.org/10.1007/s00213-011-2264-x>
- Snelleman, M. (2012). Zorg voor Rotterdamse zwerfjongeren met ernstige problematiek: goed op weg en hoe nu verder? *TSG: Tijdschrift Voor Gezondheidswetenschappen*, (3), 157–158. <http://doi.org/10.1007/s12508-012-0060-6>
- Snelleman, M., Schoenmakers, T. M., & van de Mheen, D. (2014). The relationship between perceived stress and cue sensitivity for alcohol. *Addictive Behaviors*, 39(12), 1884–1889. <http://doi.org/10.1016/j.addbeh.2014.07.024>
- Snelleman, M., Schoenmakers, T. M., & van de Mheen, D. (2015). Attentional Bias and Approach/Avoidance Tendencies Do Not Predict Relapse or Time to Relapse in Alcohol Dependency. *Alcoholism: Clinical and Experimental Research*, 39(9), 1734–1739. <http://doi.org/10.1111/acer.12817>
- Snelleman, M., Schoenmakers, T. M., & Van de Mheen, D. (in press). Relapse and Craving in Alcohol-Dependent Individuals: a Comparison of Self-Reported Determinants. *Substance use and Misuse*, 1-10.

Submitted articles

- Snelleman, M., Waters, A.J., Schoenmakers, T.M., Szeto, E., Franken, I.H.A., Hendriks V.M., and van de Mheen, D. (submitted). Craving and affect among alcohol-dependent patients trying to maintain abstinence: An Ecological Momentary Assessment study. *Psychopharmacology*
- Snelleman, M., Schoenmakers, T. M., & Van de Mheen, D. (submitted). Do coping motives moderate the relationship between anxiety, craving and drinking? *Journal of Studies on Alcohol and Drugs*.

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: M. Snelleman

Erasmus MC Department: Public Health

Research School: NIHES

PhD period: 2011-2015

Promotor(s): H. van de Mheen, PhD

Supervisor(s): T.M. Schoenmakers, PhD

1. PhD training

	Year	Workload Hours/ECTS)
General courses		
- English Biomedical Writing and	2014	3 ECTS
Specific courses		
- Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences	2011-2014	70 ECTS
Seminars and workshops		
- Basic Principles of Qualitative data	2011	24 hours
- Composite International Diagnostic Interview (CIDI)	2011	8 hours
Presentations		
Stress, implicit processes, and craving in alcohol dependence: Designing an Ecological Momentary Assessment Study (Society for Ambulatory Assessment, Amsterdam)	2013	8 hours
Een kwalitatieve studie naar de factoren voorafgaand aan craving en terugval bij alcohol- afhankelijke patiënten (23 ^e Forum Alcohol en Drugs Onderzoek, Utrecht, the Netherlands)	2013	8 hours
(40 th symposium of the Kettil Bruun Society, Torino, Italy)	2014	8 hours

- Voorspellers van terugval bij alcoholafhankelijkheid: voorlopige resultaten (24 ^e Forum Alcohol en Drugs Onderzoek, Utrecht, the Netherlands)	2014	8 hours
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(Inter)national conferences

- 3rd Biennial Conference of the Society for Ambulatory Assessment, Amsterdam,	2013	16 hours
- 23 ^e Forum Alcohol en Drugs Onderzoek, Utrecht,	2013	8 hours
- 40 th symposium of the Kettil Bruun Society, Torino,	2014	32 hours
- 24 ^e Forum Alcohol en Drugs Onderzoek, Utrecht, the Netherlands	2014	8 hours

2. Teaching

	Year	Workload
Supervising practicals and excursions,		
Supervisor Community project 4 th year Medicine students	2013	16 hours
Supervisor Community project 4 th year Medicine students at Erasmus Medical Center	2014	16 hours
