# Cue Exposure Therapy for the treatment of heroin addiction

**Cover design**
Sander F. de Wilde

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Optima, Rotterdam

Marlies A.E. Marissen, The Hague, The Netherlands, 2004. Cue Exposure Therapy for the treatment of heroin addiction. Universiteit van Amsterdam, Faculteit Geneeskunde. Thesis, University of Amsterdam.

# Cue Exposure Therapy for the treatment of heroin addiction

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. mr. P.F. van der Heijden
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Aula der Universiteit

op donderdag 24 februari 2005, te 14.00 uur

door

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geboren te Utrecht

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# Chapter 1

# Cue Exposure Therapy for opiate dependent clients

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## Abstract

Cue Exposure Therapy is seen as a potentially effective treatment for addictive disorders. Drug-dependent clients are repeatedly exposed to drug-related stimuli and prevented from using drugs in an attempt to reduce reactivity to these stimuli. The present article gives an overview of cue reactivity models on which Cue Exposure Therapy is based. An example of cue exposure practice is given, with a focus on opiate addiction. It is concluded that the few controlled studies that have been done, do not show support for Cue Exposure Therapy as an effective treatment for addictive disorders.

# Introduction

More and more, addiction is seen as a lifelong, chronic relapsing condition where stable abstinence of the substance is a difficult, long-term goal (McLellan, Lewis, O'Brien, Kleber, 2000; Hser, Hoffman, Grella & Anglin, 2001). Relapse rates of about 60% have been found among opiate abusers after residential treatment, and almost all of the initial lapses occurred within one month after leaving treatment (Gossop, Stewart, Browne & Marsden, 2002). The high relapse rates among substance dependent clients have motivated many researchers within the addiction field to search for, develop and test new potentially effective interventions to treat substance abuse disorder. Cue exposure therapy (CET), a behaviour therapy that is based on classical conditioning principles, is an example of such a therapy. The present article starts with a brief overview of some of the theoretical views concerning CET. Then, a description of cue exposure practice with (abstinent) opiate addicts is given. Finally, a review of results of earlier cue exposure studies with substance dependent clients is described.

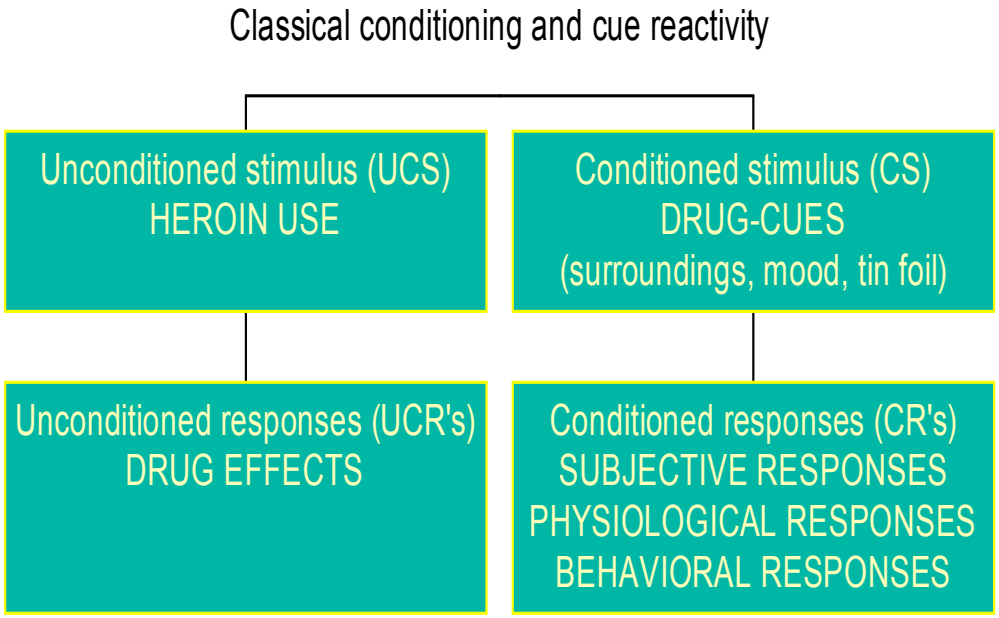
# Theoretical views

## *Conditioning principles*

In the last decades, there has been a lot of attention in substance abuse research for theoretical insights based on animal- and human models of learning. Human drug seeking behaviour is often seen as the combination of operant behaviour and classical conditioning. With operant behaviour; the response one makes is dependent on the previous experience that the person had with a particular cue. The consequence of a particular behaviour may increase or sustain the subsequent likelihood of the behaviour: it will increase when the consequence is regarded as rewarding and will reduce when the consequence is experienced as punishing (Glautier & Remington, 1995). Drugs are often acknowledged as rewarding in that they have positive hedonic effects (positive reinforcement) and that they can relief negative states (negative reinforcement).

Classical conditioning is a form of learning in which neutral stimuli become relevant and are able to evoke strong reactions as a result of the pairing with an unconditioned stimulus (UCS). An unconditioned stimulus (such as heroin-intake) is followed by an unconditioned response (UCR) such as feeling "high". In the case of

heroin users, inhaling or injecting heroin (UCS) is operant behaviour, reinforced by the positive drug effects (UCR). When this ritual is repeated often, it means that the drug user repeatedly experiences drug effects in the presence of distinctive cues. These cues, for example tin foil, needles, specific locations, or other drug users become associated with heroin-intake (UCS). This way, these originally unconditioned stimuli become conditioned stimuli (CS), which are able to evoke conditioned responses (CR) such as craving, physiological and behavioural reactions.



*Cue reactivity models*

One of the largest problems in the treatment of substance abusers is the remaining, untreated or persistent reactivity to drug related cues (Franken, de Haan, van der Meer, Haffmans & Hendriks, 1999). Studies have repeatedly indicated that both subjective and autonomic responding is present in addicts who are being confronted with drug related conditioned stimuli (Childress, Ehrman, Rohsenow, Robbins & O'Brien, 1992; Rohsenow, Niaura, Childress, Abrams & Monti, 1990). This phenomenon is called cue reactivity, a specific type of conditioned response.

Drug cue exposure can result in various conditioned responses. These responses include subjective responding (i.e., an increase in craving and negative emotions), autonomic responding (i.e., an increase in skin conductance and decrease in skin temperature) and behavioural reactivity (such as drug-seeking or actual drug use) (Drummond, Glautier & Remington, 1995; Childress, McLellan, & O'Brien, 1988; Franken et al., 1999; Carter & Tiffany, 1999).

*Figure 1 Classical conditioning and cue reactivity*

In general, craving is thought of as a "subjective state" associated with drug or alcohol dependence. Craving has been described by the WHO as "the desire to experience the effect of a previously experienced psychoactive substance" (UNDCP/WHO, 1992).

Several models have been developed, including the conditioned withdrawal model (Wikler, 1973), the opponent process theory (Siegel, 1983), outcome expectancies theory (Marlatt, 1985), and information-processing model (Tiffany, 1990), to describe the role of cue reactivity (especially craving or excessive 'drug-wanting') in relapse. A more recent model is the incentive-sensitisation model (Robinson & Berridge, 2001). In all the models, classical conditioning plays a major role suggesting that craving is the result of learning processes.

The conditioned withdrawal model states that when a person undergoes withdrawal episodes, a conditioning process occurs (Wikler, 1973). Through this process, the unpleasant symptoms of withdrawal (e.g., tremors, agitation, and anxiety) become associated with stimuli present during the withdrawal episodes (e.g., treatment settings such as hospital or therapist's office). As a result, exposure to these stimuli will induce a (mild) withdrawal syndrome, which, in turn, will result in cravings to use drugs to relieve withdrawal. Research findings and clinical observations, however, do not provide strong support for this model. For example, patients usually experience few cravings in treatment settings, and responses to

withdrawal-associated stimuli do not consistently resemble withdrawal symptoms (Rohsenow & Monti, 1999).

Siegel (1983) has focused on drug-compensatory responses. This model states that the body's repeated efforts to counter the effects of the drug and to maintain homeostasis results in compensatory responses. In the presence of drug-related cues, the body will prepare itself for the intake of drugs and will produce the discomfort of drug-opposite symptoms, which can be experienced as withdrawal or craving. As these drug-opposite responses become stronger after repeated drug-intakes, this could also be an explanation for the tolerance that is often seen with opiates and several other drug classes (Siegel, 1983).

Other theories seem to pay more attention to the cognitive aspects of cue reactivity. For example Marlatt's outcome expectancies theory tries to explain relapse by taking into consideration the positive expectancies one can have about the effects of the drug. An explanation for the occurrence of positive outcome expectancies could be the lacking of useful alternative coping strategies available for a person (Marlatt, 1985). Perhaps the occurrence of drug-opposite symptoms in the presence of drug-related cues can trigger positive expectancies about drug-effects.

A second important cognitive theory, the automatic-processing model of Tiffany (1990), proposes that much drug-seeking behaviour is controlled by automatic learned processes rather than by conscious thoughts. The use of drugs has become a habit, a process that occurs automatically and is not necessarily intentional; actions necessary for drug-use are coded in automatic action-schemes. Craving (as a non-automatic cognitive process) occurs when these schemes are disrupted either voluntary (e.g., when an individual decides to quit drugs) or involuntary, when the drug is not available (Tiffany, 1990).

The incentive sensitisation model of Robinson and Berridge (2001) states that prolonged drug-use can lead to long-lasting changes in the reward system of the brain. Through classical conditioning, the brain's reward system becomes hypersensitive towards conditioned drug-related stimuli. This focus on conditioned drug-stimuli leads to enhanced 'drug-wanting' or craving and can persist long after discontinuation of drug use (Robinson & Berridge, 1993, Robinson & Berridge, 2001).

Attentional bias, (i.e.,, the automatic (hyper) attentive response to relevant stimuli) serves as an important cognitive intermediate between conditioned drug-related stimuli, craving and relapse (Franken, 2003). Through attentional bias, drug-related cues are signalled more easily, it is more difficult to draw attention away from them and, because of limited attention capacity, processing of competitive, alternative cues

is more difficult (Franken, 2003). Similar to the automatic-processing model of Tiffany, this model proposes the existence of an automatic pathway to craving.

## Cue exposure practice

### *Cue reactivity among opiate dependent clients*

It is widely acknowledged that cue reactivity as a reaction to opiate-related stimuli is present in opiate addicts (Carter & Tiffany, 1999; Drummond et al., 1995; Childress, Hole, Ehrman, Robbins, McLellan & O'Brien, 1993; Powell, Gray & Bradley, 1993).

Craving, or the intense desire to use drugs seems to be one of the most important components of cue reactivity among opiate addicts (Carter & Tiffany, 1999b). Besides craving, other subjective cue-elicited responses can be measured in abstinent opiate abusers when exposed to drug-related stimuli (Franken et al., 1999). These reactions include subjective withdrawal symptoms, subjective drug-agonistic effects, and increasing anxiety, depression, anger and tension levels.

In addition to the subjective responses, several psycho-physiological responses are frequently reported as a result of cue-exposure. Change in electrodermal activity is a sensitive physiological indicator of psychological phenomena in cue-reactivity. Changes in skin-conductance-level and skin-conductance response are frequently measured as a reaction to drug-related stimuli (Hugdahl, 1995). For example, Hugdahl and Ternes (1981) exposed opiate-dependent subjects to either neutral film clips or film clips that showed the preparing and injection of a drug while measuring their electrodermal activity. The subjects showed increased response frequency while watching the film showing the preparing and injection of drugs. Other physiological reactions that have been investigated in this respect include heart rate, salivation, and skin temperature (Glautier, Drummond & Remington, 1992; Carter & Tiffany, 1999b). Furthermore, research has shown that even memories of craving-episodes in abstinent opiate abusers can elicit changes in regional blood flow in different brain regions (Daglish, Weinstein, Malizia, Wilson, Melichar, Britten, Brewer, Lingford-Hughes, Myles, Grasby & Nutt, 2001).

These physiological changes can persist a long period after detoxification. A study among abstinent opiate dependent subjects showed that self-reported cue reactivity was still present after 12 months of intensive drug free residential treatment (Franken et al., 1999).

The presence of cue reactivity can result in a particular vulnerability in opiate addicts and can eventually result in relapse (Carter & Tiffany, 1999b; Robbins &

Everitt, 1999). A relapse episode is often preceded by an intense craving for drug-use (Heather, Stallard, Tebbut, 1991). In addition, several studies have shown that cue reactivity is a predictor of relapse in alcoholics and drug addicts (Rohsenow, Monti, Rubonis, Sirota, Niaura, Colby, Wunchel & Abrams, 1994; Drummond & Glautier, 1994). In conclusion, evidence is available that cue reactivity is predictive of relapse in drug use and reinstatement of drug dependence among addicts (Drummond, 2000).

*Cue exposure treatment*

In the same manner that cue reactivity is acquired through principles of classical conditioning, it can be applied to extinguish cue reactivity (Drummond et al., 1995; Franken et al., 1999). In Cue Exposure Therapy (CET), detoxified addicts are exposed to drug-related cues, attempting to elicit maximal cue reactivity levels. However, instead of the usual, learned response (i.e., actual drug use), response is now prevented and the drug-related cues become associated with a new response, i.e.,, not using heroin. By doing this repeatedly, extinction of conditioned stimuli takes place and these will no longer evoke cue reactivity as represented in figure 2.

Presently we are conducting a randomised controlled cue exposure study and we will use our treatment protocol as an example of CET for opiate addicts. Subjects received a protocolized treatment, which consisted of nine, one-hour cue exposure sessions with response prevention.

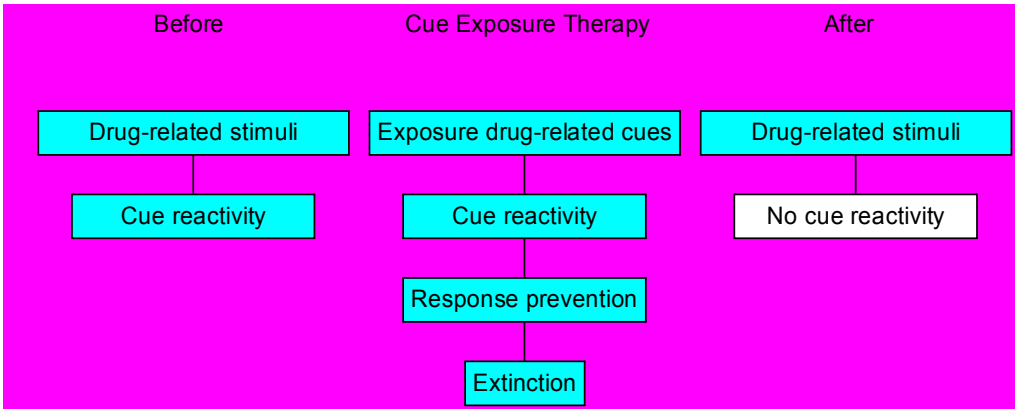



*Figure 2. Cue exposure therapy*

During the first session, highly individualized drug-related stimuli, which were able to induce craving for heroin, were examined and reported in a craving interview. The cues were often drug-paraphernalia such as actual heroin, tin foil and the performance of the ritual of preparing heroin-consumption. By means of the craving interview, not only the highly individualized cues for the subject were distinguished,

but also the interaction between co-occurring cues, the so-called "cue-cluster" (Drummond, 2000). It was also examined whether in the past cues sequentially had resulted in relapse, a so-called "cue-chain".

In addition to paraphernalia, other stimuli were used such as videotapes of drug related neighbourhoods, exposure to other drug users (either through role-play with the therapist or on video) and negative mood induction. The individualized cues were presented to the client in a hierarchic sequence; cue reactivity was first extinguished for relatively 'easy' cues, before the next cue was presented. If a particular cue only had salience for an individual in a particular context, attempts were made to mimic this context as realistic as possible. This was done for example by role-plays between therapist and client but also by offering multiple cues. Cue-chains and cue-clusters were reproduced during cue exposure sessions in order to arouse craving as highly as possible. During the sessions clients were asked to report their craving for heroin on a scale ranging from '0' ( absolutely no craving), to '10' (extremely intense craving). The therapist focused on signals of cognitive avoidance, i.e., when participants made attempts to control or temper their craving levels. Clients were instructed to remain in the situation and stay focused on the cues with full attention until extinguishing of cue reactivity took place.

At the end of each session, clients were provided with relatively simple behavioural techniques to reduce possible remaining craving for heroin. Examples of these techniques are: focusing on the negative consequences of heroin use, or focusing on the positive side of being abstinent. At the end of the last session an evaluation of the therapy took place.

## Effectiveness of Cue Exposure Therapy

Cue exposure treatment has become a method of key importance in obsessive-compulsive disorders (Hansen, Roelofs, Keijsers & Hoogduin, 1997) and in the treatment of other anxiety disorders (Mineka, Mystkowski, Hladek, Rodriguez, 1999). For other types of psychopathology, such as eating disorders and substance abuse disorders, less research has been conducted.

In the last two decades, Cue Exposure Therapy (CET) has been suggested to be a promising therapy for the treatment of addictive behaviours (Drummond et al., 1995; Conklin & Tiffany, 2002). From a clinical point of view, the most relevant measure of success for abstinent substance dependent clients is relapse prevention. This goal of continued abstinence should be reached through the mechanism of

extinction of cue reactivity. A summary of the results of randomised Cue Exposure studies is presented in table 1. Only studies that started with abstinent participants are included. This excludes all studies with nicotine addicts and moderation-oriented studies with alcoholics. The study of O' Brien et al (1990) was excluded because we were unable to determine the effect on cue reactivity and relapse (O'Brien et al., 1990). Relapse is defined as at least one-time substance use after a period of abstinence following treatment.

Earlier research suggests that cue exposure therapy with alcoholics is effective on several outcome measures. Drummond and Glautier (1994) studied 35 alcohol dependent clients who were sequentially assigned to either a cue exposure condition or to a relaxation control condition. The CET group did show a reduction in tension compared to the control group, however craving and physiological rates declined equally in both groups. The results of this study suggest that overall, the cue exposure group had a more favourable outcome than the control group in terms of latency to reinstatement of heavier drinking and dependence and in the overall quantity of alcohol consumed during follow-up. However, when abstinence would have been taken as an outcome variable, the authors conclude that there would be no difference between the experimental and control group.

McCusker & Brown found that among 16 abstinent alcoholics autonomic, but not self-reported reactivity significantly reduced after CET compared to a control group. No follow up was conducted.

Cue exposure therapy in combination with coping skills treatment has suggested to be effective with alcoholics with cue reactivity and abstinence as outcome measures (Monti, Rohsenow, Rubonis, Niaura, Sirota, Colby, Goddard & Abrams, 1993; Monti, Rohsenow, Swift, Gulliver, Colby, Mueller, Brown, Gordon, Abrams, Niaura & Asher, 2001). Monti (1993) found an effect of CET on cue -reactivity, only among high-cravers. One study found no effect of CET on cue reactivity or abstinence status, yet fewer heavy drinking days when they did drink (Rohsenow et al., 2001). However, within the design of these alcohol- CET studies it is not clear whether effects are due to the ingredient of CET or the equally provided coping skills training (Monti et al., 1993; Rohsenow et al., 2001) or communication skills training (Monti et al., 2001).

For opiate studies, control groups are scarce and results are inconsistent. In a study of Powell et al. (1993) 21 detoxified opiate addicts were randomly assigned to a) cue exposure b) cue exposure and cognitive aversion therapy or c) routine treatment alone. In the cue exposure conditions the amount of craving was significantly reduced, while in the control condition no change of craving occurred. No

follow up was conducted. In contrast, Dawe et al. (1993) did not find any significant difference in cue reactivity or relapse between CET and the control condition (Dawe, Powell, Richards, Gossop, Marks, Strang & Gray, 1993). These two studies are the most recent studies involving opiate research and cue exposure in which a control group was used. However, there are several methodological restrictions in these studies. In the first study (Powell, Gray & Bradley, 1993) only a pre-selected group of participants who reported craving were selected for analysis. Furthermore, although a control group was present, no control treatment was used to control for non-specific therapy factors such as attention from the therapist. In addition, no follow up measurement was conducted. Finally, both studies included a small study-sample and no physiological measures were taken into account.

In conclusion, of 5 studies on CET with alcoholics and only two CET studies with opiate addicts with a control group, both cue reactivity and relapse as outcome measures are available. In general, the few available studies do not support the effectiveness of CET.

For example, none of the cue exposure studies has provided sufficient evidence to conclude that CET alone reduces relapse rates in addicts. Despite the repeated failure of CET as a method to increase abstinence in drug-dependent patients (Conklin & Tiffany, 2002), on theoretical grounds it is still assumed that CET has potential merit, provided that it is offered under the right circumstances.

At the moment our cue exposure study attempts to address methodological limitations of earlier studies. The effectiveness of cue exposure therapy will be examined for opiate dependent clients in a long-term abstinence-oriented treatment. This will be done in the context of a randomised controlled trial including a sufficiently large sample size, a control therapy, in-vivo exposure to actual heroin, assessment of both self-reported and physiological measures and a three-month follow up assessment.

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*Table 1. Effects of randomised controlled cue exposure treatment*

| Year | Authors | N tot | Intervention-type | Follow up | Self-report and/or physiological measures | Effect on self-reported reactivity | Effect on Physiological reactivity | Effect on relapse |
|---|---|---|---|---|---|---|---|---|
| **Alcohol** | | | | | | | | |
| **1993** | **Monti *et al*.** | **40** | **CET+** | **3, -6 month** | **S + P** | **-** | **-** | **+** |
| **1994** | **Drummond & Glautier** | **35** | **CET** | **3-, 6-month** | **S + P** | **+** | **-** | **-** |
| **1995** | **McCusker & Brown** | **16** | **CET** | **No** | **S + P** | **-** | **+** | **?** |
| **2001** | **Rohsenow *et al*.** | **129** | **CET++** | **6-12 months** | **S + P** | **-** | **-** | **-** |
| **2001** | **Monti *et al*.** | **165** | **CET++** | **3-, 6-, 12 months** | **S** | **+** | **?** | **+** |
| **Opiates** | | | | | | | | |
| **1993** | **Powell *et al*.** | **21** | **CET** | **No** | **S** | **+** | **?** | **?** |
| **1993** | **Dawe *et al*.** | **43** | **CET** | **6 weeks, 6 months** | **S** | **-** | **?** | **-** |

CET+ = CET combined with craving-specific coping skills training

CET++ = CET combined with craving-specific coping skills training and communication skills training

S= Self-reported reactivity

P= Physiological reactivity

+ = positive effect

- + negative effect

? = unclear

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# Chapter 2:

## Outline and hypotheses of the thesis

As mentioned in chapter 1, "Cue Exposure Therapy for the treatment of opiate dependent clients", Cue Exposure Treatment as a hypothesised potentially effective treatment has a long history starting from its roots in classical conditioning theory. For the treatment of anxiety-related disorders, CET is a well-established treatment method, often the treatment of first choice. For addictive disorders, this efficacy needs yet to be shown since overall, CET studies have not been effective in reducing relapse rates among substance dependent clients. Studies have been designed integrating CET with other therapeutic elements such as coping-skills or communication-skills training, however this type of design makes it retrospectively impossible to show unique treatment effects of CET. Therefore, the 'basics' of CET will be tested in the context of a randomised controlled trial.

The main focus of the present study is to examine the efficacy of Cue Exposure Therapy (CET) on treatment outcome in a population of abstinent heroin dependent clients who are admitted to residential treatment. The research questions of this thesis will be described below.

The second part of the thesis focuses on theoretical aspects behind CET, mainly referring to the question: What *is* cue reactivity? If we want to apply an intervention which heavily relies on the mechanism of cue reactivity, we need to study its basic concept since earlier studies show that much remains unclear regarding the cue reactivity paradigm. For example, what is the relationship between elicited self-reported, subjective cue reactivity and physiological, objective cue reactivity? It is generally found that the relation between these two forms of reactivity is weak. In chapter 3, "The relation between social desirability and cue reactivity in a cue exposure paradigm" we hypothesise that social desirability might be distorting this relationship because (heroin) craving seems to be a quite sensitive subject among members in the residential therapeutic centre.

Chapter 4 "Predictors of subjective and physiological cue reactivity among opiate dependent clients" is a further exploration of the concept of cue reactivity, attempting to define individual patterns in reactivity to heroin cues. Not all abstinent drug

dependent clients show cue reactivity in the presence of drug-related stimuli. We hypothesised that individual differences in cue reactivity are present and that this is related to certain baseline characteristics of participants such as demographics, mood and personality. Therefore, predictors for self-reported and physiological heroin craving are examined.

The third part of the thesis can be seen as its central part. It describes the effects of CET on treatment outcome, starting with the main effects which are described in chapter 5 "Cue Exposure Therapy for the treatment of opiate addiction can be harmful: Results of a randomised controlled trial". We hypothesised that CET for abstinent heroin dependent clients would be an effective intervention in reducing both self-reported and physiological craving compared to a control treatment. Further, as opposed to treatment outcome in the control treatment, the extinction of cue reactivity in the CET-group would lead to less dropout of the therapeutic centre and less relapse in heroin use at follow up.

Chapter 6 "Attentional bias predicts heroin dependence following treatment" describes attentional bias as the most important determinant of relapse in our population. Attentional bias was defined as a response to heroin-related words measured by a stroop-task and is often believed to be a predictor of relapse in addictive disorders. We hypothesised that attentional bias would be reduced after CET since participants would be less 'distracted' by heroin-related words, compared to participants in the control therapy. Furthermore, we examined whether pre-treatment attentional bias was a good predictor of relapse three months later. Hereby, we controlled for the role of pre-treatment self-reported craving.

The fourth part describes what can be concluded from the results of this thesis. In chapter 7, "Cue Exposure as a practical treatment for addictive disorders: why do we keep trying?", we summarize the findings of the current study and draw some conclusions. In addition, the future of CET as an effective treatment for addictive disorders is discussed.

# PART II: ASPECTS OF CUE REACTIVITY

# Chapter 3

# The Relation Between Social Desirability and Cue Reactivity in a Cue Exposure Paradigm

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## Abstract

A low association between self-reported craving and physiological measures of craving is often found. Social desirability might influence this relation between subjective and physiological reactivity. Subjects were seventy-six in-patient abstinent heroin abusers. Social desirability, general craving scores and difference scores of physiological and subjective heroin craving, measured after exposure to a neutral and heroin cue were assessed. Cue reactivity, both subjective and physiological was found to be enhanced after exposure to a heroin-related cue. However, only a modest relation was found between subjective and physiological cue reactivity. High social desirability scores were associated with lower craving scores, but not with physiological scores. It can be concluded that, among other subject-related variables, social desirability influences self-reported craving but does not influence physiological reactivity in a clinical population. However, no significant moderation effect of social desirability on the relation between subjective and physiological reactivity was found.

# Introduction

The role of craving in addiction research has been discussed for several years now. In particular, the role of craving in drug use (after abstinence) has been subject to debate. The relation between self-reported craving and drug use is not clear. Tiffany (1990) for example, states that verbal craving reports display only a modest association, if any, with drug use. In addition, self-reported, subjective craving and physiological cue reactivity, for example skin conductance response, have generally been found to be only modestly correlated. Robbins and colleagues (1997) found that physiological variables did not predict reported drug states. These discrepancy may reflect a certain unreliability of the self-report of motivational states in general, and craving specifically. Some authors recognize this problem and have described the measurement of craving by self-report as "problematic"(Miller, 1996 ; Sayette, Shiffman, Tiffany, Niaura, Martin & Shadel, 2000). However, most studies on craving rely heavily on the self-reported data and regard self-report as the golden standard when it comes to the study of subjective experiences. Therefore, it is important to give attention to possible explanations for the discrepancy between self-reported, subjective craving and physiological measurements of cue reactivity.

One of the possible explanations for the discrepancy between subjective and physiological outcomes might be that physiological measures reflect more than craving alone. For example, frequently used measures such as skin temperature and skin conductance are also known to reflect general emotional states (Prokasy, 1973). In contrast, these psychophysiological measures may be less vulnerable to conscious control by subjects and are a frequently used tool in the requirement of more objective measurement among subjects (Sayette et al., 2000).

Another possible explanation of the discrepancy between self-reported craving and physiological measurements could be response bias in the direction of social desirable answers on questionnaires**.** Since the early 1930s, the concept of social desirability has been a topic of concern for researchers and practioners (Stober & Munch, 2002). Several studies have shown that people tend to give answers to questionnaires more according to a social norm than to the actual situation (Sjostrom, 2002). This tendency is named social desirability. Social desirability has been defined as “answers, which reflect an attempt to enhance some social characteristics or minimize the presence of some socially undesirable characteristics

(US Department of Health, 1977). It has been stated that there is a tendency in people to “assert good and deny bad” and that the “deny bad" part is found to be more common in self-report (DeMayo, 1984). Social desirability response bias seems to be occurring mostly when there is a high need for social approval (Cox, Swinson, Direnfeld & Bourdeau, 1994), and when the questions concern “sensitive subjects’ such as smoking, alcohol consumption and sexual behaviour (Sjostrom, 2002). For example, it was found that a high need for social approval was associated with minimizing self reported alcohol abuse by subjects as opposed to reporting an anxiety disorder (Cox et al., 1994).

In the current sample under study, the criteria of the presence of a sensitive subject and the need for social approval seems to be present. The subjects are admitted to an abstinence-orientated therapeutic community where the group members are dependent on each other for their progress and recovery. Furthermore, the social norm of this treatment setting seems to be directed towards cue-avoidance. In the current study, before and after being confronted with heroin cues, subjects are asked to report their levels of craving (desire, tendency to use) for heroin. This subject might be considered to be a taboo in the therapeutic community. Although this influence of social desirability has been hypothesized many times (see Baker & Brandon, 1990; Sayette et al., 2000), up to date only one study addressed this relationship in craving research (Rohsenow, Monti, Abrams, Rubonis, 1992). In this study it was found that, after correcting for level of alcohol dependence, social desirability was unrelated to both subjective as well as physiological cue reactivity.

The present study attempts to further examine the role of social desirability among an in-patient sample of abstinent opiate addicts in relation to their cue reactivity. First, it is examined whether craving and skin conductance within abstinent opiate abusers increase as result of exposure to a heroin-related cue. Second, relations between self-reported craving and the skin conductance measurements are being examined. Third, the hypothesis is tested that social desirability is associated with self-reported opiate craving, and not with physiological measures. And fourth, it is being examined whether the interaction between social desirability and self-reported craving moderates the relation between these two variables and skin conductance.

## Materials and methods

### *Subjects and setting*

The present study is part of a larger randomised controlled trial testing the effectiveness of cue exposure therapy. The current study sample consists of 76 participants who- after successful opiate-detoxification- have been admitted to an in-patient substance abuse treatment program of Parnassia Psychiatric Center in The Netherlands. To be included in the study, the participant must (a) be heroin dependent (DSM-IV; APA, 1994), (b) have administered heroin primarily through intravenous injection or through inhalation, (c) be at least 18 years old, (d) have sufficient understanding of the Dutch language, and (e) have given written informed consent. Clients with suicidal ideation or psychotic symptoms were excluded from the study.

### *Instruments and physiological recordings*

The Addiction Severity Index (ASI) was used to describe participant's characteristics such as demographics and drug use (McLellan, Luborski, Woody, & O'Brien, 1980). The instrument has good reliability and validity of scales (Hendriks, Kaplan, Van Limbeek, & Geerlings, 1989; McLellan et al., 1980).

Because there is no general accepted measure of craving (Kozlowski, Pillitteri, Sweeney, Whitfield & Graham, 1996; Sayette et al., 2000; Tiffany, Carter, & Singleton, 2000), three different measures of craving were applied. First, a single item visual analogue scale was employed. The Visual Analogue Scale (VAS) measures a subject's current craving level for heroin on a 100-mm line labelled "not at all" at one end and "extremely" at the other end. The subject has to indicate how much current craving he/she experiences at that moment. The result is a score on a continuous scale ranging from 0 to 100. In addition, two multi-item questionnaires, the Obsessive-Compulsive Drug Use Scale (OCDUS) and Desire for Drug Questionnaire (DDQ) were employed (Franken, Hendriks, & Van den Brink, 2002). The three OCDUS scales (thoughts about heroin and interference, desire and control over heroin use, and resistance to thoughts and intention to use heroin) measure general craving within a time frame of a week. Subjects are asked to respond to 15 questions on a 5-point scale. All proposed scales have good reliability and concurrent validity (Franken et al., 2002). The OCDUS scales thoughts and interference, and desire and control, measure what is believed to be the core element of this study; the

actual general craving or desire for heroin. The scales have an internal consistency of $\alpha$=. 90 and $\alpha$=. 84 respectively. These two scales are examined in this study.

The DDQ, which measures current craving, is a translation of the Desires for Alcohol Questionnaire (DAQ) (Love, James, & Willner, 1998) and adapted for drug use (Franken et al., 2002). The DDQ consists of 14 questions with scores ranging on a 7-point scale. The DDQ measures three factors: desire and intention to use drugs, negative reinforcement (items that reflect the relief of negative states), and perceived control over heroin use. The three scales of the DDQ have good test-retest reliability and concurrent validity ($\alpha$= .81 for the desire and intention to use scale). Since only the DDQ-desire scale is assumed to measure actual craving for heroin, only this scale is included in the study's design.

Social desirability was measured with the "Lie Scale" or "Social Desirability Scale" of the Eysenck Personality Questionnaire Revised Short Scale (EPQ-RSS) (Eysenck & Eysenck, 1975) This scale measures the degree in which people tend to answer questionnaires in a socially desirable manner.

The short version of the EPQ (EPQ-RSS) is used because of its good validity and reliability of scales and its convenience of use in comparison to the long version (Sanderman, Arrindell, Ranchor, Eysenck, & Eysenck, 1991). The social desirability scale of the EPQ-RSS has an internal consistency of approximately $\alpha$=.70 (Sanderman et al., 1991).

Finally, in the present study skin conductance was used as an indicator of physiological reactivity. Two different types of electrodermal measures were used: (1) average change scores of mean skin conductance level (SCL in µSiemen) when exposed to the neutral versus heroin cue were used (Δ SCL), and (2) skin conductance response (SCR) measuring phasic responses that reflect the sudden impact of a discrete stimulus. The average change scores of total count of waves when exposed to the neutral versus the heroin cue were measured (Δ SCR). Skin conductance has been found to be an adequate measure of physiological reactivity in opiate addicts (Hugdahl & Ternes, 1981; Childress, McLellan & O' Brien, 1988). Electrodermal responses on both a neutral and heroin video were measured by Contact Precisions Instruments and Psylab software. The electrodermal response was recorded using two bipolar placed Ag-AgCl electrodes attached to the medial phalanx of the middle and index finger of the non-dominant hand.

*Procedure*

After two weeks following admission and detoxification in the drug-free therapeutic setting, the baseline measurement for this cue-exposure study was conducted. After signing informed consent, demographic and addiction related variables were assessed by the ASI interview and OCDUS. After this, subjects were prepared for the physiological measurements, and all electrodes were attached. To standardize the start of the assessment-procedures, all subjects first viewed a neutral video, consisting of pictures of landscapes, for five minutes. During the video, physiological reactions were measured. Following this neutral video, baseline subjective craving (DDQ and VAS) were assessed. Subsequently, the subjects watched a drug-related video of five minutes duration, which depicted heroin users preparing their heroin and actually using heroin. Physiological reactions were again measured while watching the video. Two different videos were available as a craving-eliciting cue, dependent on the preferred route of heroin administration (smoking or injecting) of the subject watching. Immediately following the drug-video, subjective craving was again assessed (DDQ and VAS).

*Statistical analysis*

In order to investigate the relation between social desirable answering and self-reported craving, we used the craving score measured before cue-exposure (OCDUS scales), and the change score measures reflecting craving responses to the heroin cue minus the craving response to the neutral cue (Δ DDQ, Δ VAS). Also, change scores were used in examining the physiological response of subjects towards the craving-eliciting cue (Δ SCR, Δ SCL). Pearson's correlations were used to investigate all associations. Correlations between the EPQ social desirability scale, self-reported craving and physiological measures were calculated using Pearson's correlation coefficient. Furthermore, to investigate whether the interaction between social desirability and self-reported craving moderates the relation between these two variables and skin conductance, regression analysis was performed. Skin conductance served as dependent variable, and the craving and social desirability as independent variables. In the first step of the analysis, the desire and control scale of the OCDUS and social desirability were entered into the regression, in the second step the interaction term between both variables was entered in order to study the moderation effect. A significant increase in R square would indicate that the

interaction between craving and social desirability has a moderating effect on cue-reactivity.

## Results

Of the present sample, 92 % of participants were male, 79 % were of Dutch nationality, 10 % of Moroccan background and 11 % of an other nationality. The average period of heroin use among subjects was 9,3 years. Cocaine use was very common (97 %), with an average of 8,6 years of consumption. The predominant route of self-administration of heroin was smoking (90 %), and only a small minority of subjects injected their heroin (10%). A number of participants was using medication during the study (36%).

Table 1 shows that cue reactivity among subjects was found after exposure to the heroin-related video. Subjects reported an increase of feelings of desire for heroin after being exposed to a heroin-related videotape. Furthermore, after this craving-eliciting cue, physiological reactivity significantly increased on both types of electrodermal measurements.

**Table 1. Cue reactivity**

| | After neutral video M (sd) | After heroin video M (sd) |
|---|---|---|
| DDQ desire | 11.4 (5.7) | 15.8 (9.9)** |
| VAS | .92 (1.3) | 3.2 (2.8)** |
| SCL | 2.2 (1.6) | 3.4 (2.5)** |
| SCR | 17.8 (11.9) | 28.4 (13.2)** |

* = p< 0.05, ** = p< 0.01 (Paired samples T-test)

The correlations between self-reported craving and physiological cue reactivity are displayed in table 2. A significant relation between subjective craving and the physiological data could be observed. However, this relation seems to be restricted to general craving (measured over the past week) as opposed to current craving, immediately after the viewing of the videos.

Furthermore, table 2 shows that significant negative correlations were found between the "social desirability" scale and both types of self-reported craving; general as well as current craving. This means that a higher social desirability trait was associated with lesser increase in self-reported craving following cue exposure. As expected, social desirability was not significantly associated with any of the physiological measures (SCL and SCR). In the first step of the regression analysis, we entered OCDUS desire and control (since the highest correlations were found between this scale and SCR) together with social desirability in the model with Δ SCR as dependent variable. (F =3.85, df = 73; *p* = .03, with an R square of .10. and Beta coeficients for OCDUS desire and control (ß = .30; *p* =.01); and for social desirability ß=.05, *p* = .70). When entering the interaction term (between OCDUS desire and control and social desirability) in the second step of the regression (F=2.67, df =73; *p* =.054), with a ß of .07 for the interactionterm (*p = .54),* the R squared change of .01 was not significant (*p* = .54).

Table 2. Correlations between self-reported craving, skin conductance and social desirability

| | Δ SCL | Δ SCR | Soc Des EPQ-RSS |
|---|---|---|---|
| OCDUS- Thoughts and interference | .09 | .27* | -.20 |
| OCDUS- Desire and control | .13 | .31** | -.29** |
| Δ VAS | .08 | .22 | -.25* |
| Δ DDQ- Desire and intention | -.01 | .23 | -.26* |
| Δ SCL | | | .11 |
| Δ SCR | | | -.11 |

* Correlation is significant at the .05 level

** Correlation is significant at the .01 level

## Discussion

In the present study it was found that abstinent heroin addicts respond towards a heroin related stimulus with an increase of cue reactivity. This increase in cue reactivity was found both in higher subjective current craving levels, as well as in an increase in physiological reactivity towards a heroin-cue.

However, the relation between self-reported craving and physiological measurements was found to be only modest and restricted to general craving as occurred during the past week. This suggests that a person's general craving level could sensitise his reaction towards a craving-eliciting cue. Surprisingly, changes in current craving as reflected in the DDQ-desire scale and the VAS, did not correlate at all with changes in physiological measures, although it can be considered to measure the core element of craving; the desire or craving to use heroin. The question remains why no correlations were found between self-reported current craving levels and the physiological measures, as opposed to general craving.

We hypothesized that one of the possible intervening factors might be social desirability; the tendency to answer questions in a way more acceptable according to the social norm rather than to the actual situation. Negative correlations were found between self-reported craving and social desirability. More social desirability results in reporting less craving. These results were found for both types of craving; general craving over the past week and current craving as a result of the heroin-related cue. As expected, no significant relations were found between physiological measures of cue reactivity and social desirability.

These results indicate that, at least in a clinical setting, the self-reported craving is influenced by the tendency to answer in a social desirable manner. Some general studies on self-report found that in subjects with a high "social desirable answering style" (or repressive coping style) the correlation between self-report and physiological arousal is less robust than in subjects with low scores on these scales (Asendorpf & Scherer, 1983; Gudjonsson, 1981). However, comparable results were not found in the present study, since social desirability did not moderate the relation between physiological and subjective reactivity.

Traditional psycho-physiological measures may not be able to reflect motivational states (Baker & Brandon, 1990). As mentioned earlier, physiological instruments may measure more than craving exclusively, may reflect for example mood states.

It might be that the increase in self-reported craving after the craving-eliciting video might not be the actual result of this video but of the occurrence of a re-test effect. However, this is unlikely since there is also a similar increase of physiological cue reactivity after the heroin video, which cannot be explained by the occurrence of a re-test effect. An alternative interpretation of the negative relation between social desirability and craving could be that subjects who are highly pre-occupied with their craving, are less inclined to respond in a socially desirable manner. This explanation, though, is also unlikely. If subjects were not influenced at all by their tendency to respond in a social desirable manner because of their pre-occupation with craving, craving scores should represent their actual craving level, not biased by their attempts to enhance their self-presentation. If this was the case, no relationship between craving and social desirability should be found.

The findings in this study have implications for craving research. Most studies that examine the relation between craving and relapse rely heavily on self-report. The value of these self-reports concerning craving should not be underestimated since the subjective experience of craving can differ from the physiological reactions one shows. It might be that this subjective experience is equally important as a predictor of (future) drug use then are the physiological responses of clients. Despite this, the present results indicate that these self-report measurements cannot serve as the only measurement for craving. Like other motivations, self-report is influenced by other factors such as task demands, treatment demands, and social demands. As in self-reported craving, the relation between traditional psycho physiological measures - such as heart rate, temperature and skin-conductance - and relapse is not always present. Craving research is in need of new measurements that are more capable to

catch the core of craving than these traditional physiological measures. Sayette et al. (2000), Franken, Hulstein, Stam, Hendriks, & van den Brink, (in press) provide some interesting candidates, such as EEG and startle reflex.

In consideration of the negative relation between social desirability and craving, it may be concluded that craving is probably underreported in a clinical abstinence orientated treatment setting. The current sample originates from a traditional drug-free therapeutic community. It may be that the occurrence of craving is not accepted among staff and other clients. Moreover, subjects with a tendency to react in a socially desirable manner could be more sensitive to the "public opinion" within a treatment setting.

In order to draw firm conclusions on the specificity of the current findings, the relation between craving and social desirability should also be studied in non-treatment populations or treatment populations in which there is no taboo on experiencing craving. It is hypothesized that opiate users who are not in abstinence-oriented treatment are less influenced by social desirability when reporting craving.

It is known from several studies that craving plays an important role in the process of relapse (Heather, Stallard & Tebbut, 1991). In addition, researchers should make efforts to ensure that the response of craving is accepted within treatment settings, both among members of the staff and among clients themselves. Within our experimental setting it is frequently observed that clients say:" I don't experience craving because I am in treatment and I want to quit". This kind of reasoning makes clear why some clients underreport the experience of craving because this may be experienced as some kind of failure. Furthermore, factors as embarrassment and fear of the consequences of possible detection may play a role in this kind of measurements (Gudjonsson, 1982). Both treatment and research staff should make efforts to discuss this kind of misinterpretations. In future studies, beliefs of craving among both treatment staff and clients should be studied in order to verify this experimental data.

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# Chapter 4

## Predictors of subjective and physiological cue reactivity among opiate dependent clients

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### Abstract

After a period of abstinence of drug use, many drug dependent clients experience intense desire and/or physiological reactivity in the presence of drug-related stimuli. Several studies have focused on baseline characteristics, which distinguish individuals (most) susceptible in responding to drug-related cues. However some fail to make a clear distinction between self-reported craving and physiological reactivity. In the present study we examined the relationship between baseline characteristics and subjective and physiological cue-elicited reactivity among abstinent opiate dependent clients. Cue-elicited subjective and physiological reactivity were unrelated. We found subjective craving to be predicted most strongly by self-efficacy while for physiological reactivity (i.e., skin conductance response) most important predictors were years of heroin use and hostility. The fact that not only are subjective and physiological reactivity unrelated to one another, but also that these variables were predicted by distinct factors, indicate that these responses to substance-related cues represent different aspects of the addiction process.

# Introduction

Cue reactivity is the responding of (abstinent) addicts to stimuli associated with drug-use. Cues that were originally neutral (e.g., a particular neighbourhood or drugparaphernalia), can become predictive of drug use when the drug user experiences the effects of the drug in the presence of these cues. Through this process of classical conditioning, drug-related stimuli or "cues" can trigger reactivity such as craving for drugs. These conditioned responses to drug-related cues are repeatedly and consistently shown to be present in addicts (Rees & Heather; Carter & Tiffany; Franken, de Haan, van der Meer, Haffmans & Hendriks, 1999). The cue reactivity paradigm is applied often in addiction research because it is based on clear theoretic assumptions concerning the nature of drug-seeking behaviour (Drummond, 2000). However, the exact nature of cue reactivity is still unclear. For example, why do certain individuals respond to drug-related cues with increased reactivity while others do not seem to be affected at all? Studies among opiate addicts have shown that some of them are not responsive to drug-related cues (McLellan, Childress, Ehrmann & O'Brien, 1986; Kasvikis, Bradley, Powell, Marks, & Gray, 1991; Powell, Bradley & Gray, 1992). There seems to be a substantial individual variability and susceptibility for cue reactivity. Perhaps certain individuals have certain vulnerability in responding more heavily to drug related conditioned cues (Rees & Heather, 1995).

Several individual factors have been shown to be associated with cue reactivity, including mood, level of dependency, personality and self-efficacy (Rees & Heather, 1995). Generally, negative mood states are associated with increased self-reported cue reactivity (Rohsenow, Monti, Abrams & Rubonis, 1992; Greeley, Swift & Heather, 1992). In a recent study among alcoholics, it was found that the most powerful predictor of self-reported craving to drink was negative mood state, such as anger or anxiety (Litt, Cooney & Morse, 2000). Low self-efficacy has been found to be associated with self-reported craving in current drinkers of alcohol (Greeley et al., 1992).

In contrast to predictors of self-reported, subjective cue-reactivity, higher levels of dependence are more often associated with physiological cue reactivity (Rohsenow et al., 1992; Glautier & Drummond, 1994). Personality has been associated with both

self-reported craving (Powell et al., 1992; Reuter & Netter, 2001). and physiological reactivity (McCusker & Brown, 1995).

While many factors have been found to influence drug-related cue reactivity, it remains unclear how these variables interact and which predictors are most important in explaining cue reactivity in abstinent drug dependent clients. We know that self-reported and physiological cue reactivity are generally weakly related (Carter & Tiffany, 1999). Despite this, many studies fail to make a clear distinction between subjective and physiological reactivity (e.g., Glautier & Drummond, 1994; Reuter & Netter, 2001), examine only subjective cue reactivity as an outcome measure of cue reactivity (e.g., Powell et al., 1992; Greeley et al., 1992; Litt et al., 2000) or consider autonomic responsivity as a predictor of self-reported craving instead of a dependent variable (McCusker & Brown, 1995). To conclude, there seems to be a lack of studies that report on the predictors of both subjective and physiological cue reactivity simultaneously. In the present study among abstinent opiate dependent clients, the strongest predictors of self-reported and physiological cue-elicited cue reactivity were examined.

## Method

### *Participants*

Participants were admitted to a residential drug-free therapeutic centre of Parnassia Mental Health Institute in The Hague, the Netherlands. Clients were successfully detoxified and abstinent from heroin for at least two weeks before entering the study. To be included in the study, the participants had (a) to be opiate dependent (APA, DSM-IV, 1994), (b) have administered heroin primarily through intravenous injection or inhalation, (c) be at least 18 years old, (d) have sufficient understanding of the Dutch language, and (e) have provided written informed consent. Exclusion criteria were current psychosis and suicidal ideation.

## Assessments

### *Predictor variables*

Addiction Severity Index (ASI): The ASI was used to examine baseline characteristics of participants and the number of years of regular heroin use. The ASI

is a semi-structured interview with good reliability and validity (McLellan, Luborski, Woody & O'Brien, 1980; Hendriks, Kaplan, van Limbeek & Geerlings, 1989).

Eysenck Personality Questionnaire Revised Short Scale (EPQ-RSS): (Eysenck & Eysenck, 1985). This short version of the EPQ-R (48 items) includes three personality-trait scales which measure the dimensions Psychoticism (P), Extroversion (E), and Neuroticism (N). High P scores are associated with anti-social behaviour, hostility and reduced fear. High E scores are characterized by outgoing behaviour and optimism, while high N scores tend to reflect emotional instability and are associated with higher levels of anxiety and depression (Eysenck & Eysenck, 1985).

Symptom Checklist-90-Revised (Derogatis, 1994). The SCL-90 is a self-report questionnaire, designed to measure nine dimensions of psychopathology occurring in the past week. Subjects rate 90 items on a five-point scale of severity. Most important for this study are the three scales Anxiety, Hostility, and Depression since these scales measure mood-related symptoms.

Self-Efficacy List for Drug Users (SELD): The SELD was originally based on the scale of drinking habits (Walburg & van Ernst, 1985), and adapted for drug use. The list has 22 items and is a reliable and valid instrument for measuring self-efficacy in specific situations. Three dimensions describe self-efficacy to refuse drugs in risk-situations: environmental factors (e.g., when other people offer me drugs), negative moods (e.g., when I feel sad), and positive moods (e.g., when I am happy) (de Weert-van Oene, Breteler, Schippers & Schrijvers, 2000).

*Cue reactivity assessments*

Desires for Drug Questionnaire (DDQ): The DDQ measures three dimensions of current craving: desire and intention to use heroin, negative reinforcement of heroin use, and control over heroin use. The DDQ originally derived from the 14-item Desires for Alcohol Questionnaire (DAQ); (Love, James & Wilner, 1998) and was adapted for heroin use (Franken, Hendriks & van den Brink, 2002). The instrument was found to have good reliability and concurrent validity (Franken et al., 2002). In this study only the 'desire scale' was used, since it is the most direct indicator of current heroin craving (e.g., "I want heroin so much I can almost taste it").

Physiological reactivity: Skin conductance response (SCR) represents the mean number of skin conductance waves observed during a specified time-interval and has been found to be an adequate measure of physiological reactivity in opiate addicts

(Hughdahl & Ternes, 1981). Skin conductance was measured by a 24-bit digital amplifier (Contact Precision Instruments), using electrodes placed on the non-dominant hand of the subject and processed using PSYLAB analysis software (PSYLAB 7, Contact Precision Instruments).

## Procedure

First, participants received information concerning the study and signed an informed consent form. Subsequently, baseline characteristics (ASI), personality (EPQ-RSS), self-efficacy (SELD) and mood (SCL-90) were assessed. Next, participants were exposed to a 5-minutes 'neutral' video, depicting a landscape. After assessing self-reported cue reactivity in reaction to this neutral cue, a cue-reactivity eliciting video was displayed. This video showed a heroin user, either smoking or injecting his heroin, depending on the preferred route of heroin-intake of the participant in order to maximize cue reactivity levels. In addition, during this video, vaporized heroin was used as an additional olfactory cue. During both videos, skin conductance responses (SCR) were measured. Self-reported craving (DDQ) was assessed immediately after each video.

## Data analysis

Data analysis was performed on 92 of the 127 participants with a complete dataset (72% response). First, Pearson correlations were calculated between self-reported (DDQ desire) and physiological (SCR) cue reactivity, on the one hand, and mood (depression, anxiety, hostility), level of dependency (number of years regular heroin use), personality (neuroticism, psychoticism, extroversion) and self-efficacy (environmental factors, negative moods, positive moods) on the other hand. Second, a regression analysis was performed with self-reported craving (DDQ) and physiological reactivity (SCR) as dependent variable and all possible predictors (SCL-90, ASI, EPQ-RSS, SELD) as independent variables.

Variables that were significantly related to cue reactivity ($p \leq .20$) were entered into a multiple regression model using forced entry method; in order to establish their contributions to the model.

# Results

*Sample characteristics*

Of the participants, 87% were male and mean age was 32.9 years (sd =7,1 years). Most participants (84%) were of Dutch nationality. Generally, participants had a long history of drug use and reported problems over a wide range of life areas. Mean age of onset of regular heroin use was 21.8 years (sd =5,9 years) and mean number of years of regular heroin use was 8.5 years (sd=6,7 years). Most participants were poly-drug users, i.e., 93.1% used cocaine next to heroin. The usual way of using heroin was smoking (91%) while 9% predominantly injected heroin. One third of the participants were in prison before being admitted to residential drug-free treatment (31.5%). Psychological problems in the month before admission were frequently reported, by 75% of participants.

*Cue reactivity*

A considerable number of participants failed to respond with reactivity to the drug-related cues. For self-reported craving on the DDQ, 43,5% of participants reported no craving. In addition, cue-elicited physiological responding (SCR) was absent in 22,8% of participants. It was found that skin conductance was not significantly related to self-reported craving on the DDQ (r =.15; *p* =.16).

*Relation between predictors and cue-reactivity*

Table 1 shows that self-reported craving as a response to the heroin-related cue was associated with self-efficacy (environmental factors, negative and positive mood) and with hostility.

An increase in skin conductance response as a result of the heroin-related cue was associated with the number of years of heroin use, anxiety and hostility, but not with personality and self-efficacy.

*Predictors of cue reactivity*

For the first regression analysis we included the change scores on the DDQ as dependent variable. Variables, which correlated significantly with the DDQ, were entered into the regression model (SCL-90: hostility; SELD: Environmental factors, Negative moods, Positive moods). When entering in a forced entry multiple regression model, the total variance explained was 16% (R=.39, *p*=.000). Only SELD

environmental factors contributed significantly to the model (ß=-3.28, t=-2.74; *p* =.008). All other variables were non-significant.

For the second regression analysis with SCR as dependent variable, we again entered the variables in to the model which correlated significantly with the dependent variable, i.e., anxiety and hostility measured by the SCL-90 and years of regular heroin use, measured by the ASI. The total variance explained was 20% (R=.45, *p* =.000). Years of heroin use (ß =-.27, t=-2.84; *p* =.01), and hostility (ß =.25, t=2.31; *p* =.02) contributed significantly to the model. Anxiety did not significantly contributed to the model.

**Table 1 Correlations between baseline variables and cue reactivity**

| | Δ DDQ Desire | Δ SCR |
|---|---|---|
| Years of heroin use | -.19 | -.30** |
| Mood: | | |
| Depression | .02 | .14 |
| Anxiety | .03 | .27** |
| Hostility | .21* | .32** |
| Personality: | | |
| Psychoticism | .18 | .06 |
| Neuroticism | -.00 | -.08 |
| Extroversion | -.13 | .19 |
| Social Desirability | -.15 | -.04 |
| Self-efficacy: | | |
| Environmental factors | -.35** | -.05 |
| Negative moods | -.22** | -.07 |
| Positive moods | -.22* | -.10 |

* Correlation is significant at the .05 level

** Correlation is significant at the .01 level

## Discussion

The current study shows that self-reported and physiological cue reactivity to heroin related cues not only are not correlated but also that these constructs have different predictors. In the present sample of abstinent opiate dependent clients, self-efficacy was found to be the most important predictor of self-reported heroin craving. Number of years of regular heroin use and hostility were the strongest predictors of skin conductance response to the heroin stimulus.

In a psychobiological model of craving for alcohol (Verheul, van den Brink & Geerlings, 1999) it is stated that subjective craving is preceded by some (physiological) biochemical deficiency or imbalance. The absence of a relation between subjective and physiological cue reactivity in this study suggests otherwise. Besides the extensive literature showing that physiological and subjective reactivity are weakly related (Carter & Tiffany, 1999), in the present study we additionally found physiological and subjective reactivity to be predicted by different factors, suggesting different pathways leading to both types of reactivity.

Comparable to what is found in earlier studies (Greeley et al., 1992; Heather, Tebbut & Greeley, 1993), self-reported craving was negatively associated with self-efficacy, and positively with negative mood states. The perceived ability to resist heroin in risk-situations (SELD environmental factors) was the only significant predictor. In this context this means that participants who felt less able to resist heroin in drug-related risk-situations, experienced more desire for heroin as a reaction to a heroin stimulus. These findings are in line with a more cognitive reinterpretation of conditioning models within the cue exposure paradigm. Bradizza, Stasiewicz and Maisto for example, state that cognitions, such as self-efficacy, can operate as conditioned stimuli capable of eliciting conditioned responses (Bradizza, Stasiewicz & Maisto, 1994). For example, when a person experiences the positive effects of heroin repeatedly in a state of low-efficacy, these cognitions can become conditioned stimuli themselves and therefore may result in cue reactivity. This suggests a cognitive pathway leading to subjective cue reactivity.

Some findings in the present study seem difficult to interpretate. In contrast to what is generally found in studies on personality in craving (McCusker & Brown, 1991; Powell et al., 1993), neuroticism or extroversion were not significantly related to either self-reported or physiological reactivity.

And, while it is generally assumed that level of dependence is positively associated with cue reactivity (Rees & Heather, 1995; Litt et al., 2000), we found a negative relationship. It could very well be that years of regular drug use is not an accurate measure of level of dependency, since it is an indirect measure of dependence. McCusker & Brown also examined years of regular use among alcoholics and found no association between years of regular drinking and either subjective or physiological reactivity (McCusker & Brown, 1991). Alternatively, perhaps those individuals with a longer drug use career, had experienced more 'natural' exposure and possibly habituation to drug-related stimuli, and therefore physiologically responded less to a heroin-related stimulus.

While most studies found a relation between negative mood states and self-reported craving, in this study hostility was found to predict skin conductance reactivity. This is in line with findings of Rohsenow et al. (1992) who found that salvitory cue- reactors reported higher depression scores than did salvitory-non reactors, suggesting a possible relation between mood and physiological reactivity (Rohsenow et al., 1992). Given these findings, it cannot be excluded that skin conductance partly reflects general emotional states (Prokasy, 1973).

A considerable number of participants did not respond with an increase in either self-reported or physiological reactivity to a heroin-related stimulus. The absence of cue reactivity, both self-reported and physiological, in more than one third of our participants is in line with results from earlier cue reactivity studies among opiate addicts (McLellan et al., 1986; Kasvikis et al., 1991; Powell et al., 1992). It might be that our heroin stimulus was not realistic enough to elicit cue reactivity in all participants. From this point of view, virtual reality to evoke cue reactivity may offer new possibilities in cue reactivity research (Kuntze, Stoermer, Mager, Roessler, Mueller-Spahn & Bullinger, 2001). In addition, other measures of reactivity may provide a more accurate and objective representation of cue reactivity, such as PET or fMRI (Hommer, 1999).

To conclude, we hypothesized that subjective craving and physiological cue reactivity are independent constructs predicted by different factors. Some of the cue reactivity to a heroin stimulus was explained by self-efficacy, mood, level of dependence and self-efficacy, respectively 16 % for self-reported craving and 20% for skin conductance response. This means that most of cue reactivity could not be explained by these variables and research should focus more on developing assessments that are more capable in catching the core of what makes an individual respond to drug-related stimuli.

The possibility of different pathways leading to either subjective or physiological reactivity also suggests the need of developing separate interventions aiming at both types of reactivity. While some factors associated with increased cue-reactivity are difficult to influence through therapeutic interventions (e.g., personality), others are known to be altered through therapeutic techniques (e.g., self-efficacy).

More research should clarify the role of subjective, self-reported reactivity and physiological reactivity as predictors of relapse. A better understanding of individual differences, taken into account the discrepancy between subjective and physiological cue reactivity, might lead to the development of intensive interventions designed specifically around individual risk factors. This very well could contribute to more effective treatments for individuals with addiction-related problems.

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# PART III: EFFECTS

# Chapter 5

# Cue Exposure Therapy for the treatment of opiate addiction can be harmful: Results of a randomised controlled trial

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## Abstract

Persistent cue reactivity to drug-related stimuli is a well-known phenomenon among abstinent drug users, even after long periods of abstinence, and is found to be a predictor of relapse. Cue Exposure Therapy (CET) aims to reduce this cue reactivity by exposing abstinent drug users to conditioned drug-related stimuli while preventing their habitual response, i.e., drug-use. By doing so, it is hypothesised that dropout and relapse rates can be reduced among abstinent heroin dependent clients, admitted in a residential drug-free setting. Participants were randomised into either a CET- or a control group in which they were provided with placebo-psychotherapy (PPT). Self-reported and physiological cue reactivity was assessed at baseline and post-treatment. First, it was examined whether CET would lead to a decrease in drug-related cue reactivity compared to PPT. Second, the effect of CET on dropout of residential treatment and relapse into heroin use at three-month follow up was examined. It was found that both groups responded with a similar decrease in self-reported cue reactivity (both craving and mood). The CET group did show a significant decrease in physiological reactivity compared to PPT. However, change in cue reactivity to heroin-related stimuli had no effect on dropout and relapse rates; these were significantly higher in the CET group. This is the first randomised controlled trial that shows that Cue Exposure Therapy might increase dropout and relapse rates among abstinent heroin dependent clients in a drug-free setting and thus might be harmful in this specific population.

# Introduction

High dropout and relapse rates are one of the most prominent problems in addiction care to such a degree that some consider addiction as being a chronic disease (McLellan, Lewis, O'Brien, Kleber, 2000). Compared to other types of substance abusers, opiate addicts have the highest dropout rates (e.g., De Weert-van Oene, Schnabel & Schrijvers, 1998). rates after treatment, defined as the return to drug use after a period of abstinence, are high and longitudinal heroin use patterns are remarkably stable among opiate abusers (e.g., Gossop, Stewart, Browne & Marsden, 2002; Hser, Hoffman, Grella & Anglin, 2001). One of the explanations for these unoptimistic figures is that drug users can experience intense and persistent cue reactivity in the presence of drug-related stimuli, even after long periods of abstinence (Drummond, Glautier & Remington, 1995; Franken, de Haan, van der Meer, Haffmans & Hendriks, 1999; Carter and Tiffany, 1999).

When drug-related stimuli, such as paraphernalia, become repeatedly associated with drug-intake, these stimuli can eventually become conditioned stimuli that are able to evoke strong reactions. In other words, in the case of opiate addiction, when the opiate user experiences the positive effects of heroin intake repeatedly in, for example a certain neighbourhood, this formally neutral neighbourhood can become a conditioned stimulus (CS) and therefore be able to evoke conditioned responses such as cue reactivity and relapse to drug use (CR). Exposure to these conditioned stimuli can evoke strong reactions in the drug user, such as craving for heroin, and physiological symptoms. In a meta-analysis of cue reactivity studies, it was found that drug users generally respond to drug-related cues with increased self-reported craving, increased sweat gland production and a decrease in skin temperature (Carter and Tiffany, 1999). In some studies this persistent cue reactivity following drug-related cues was found to be a predictor of relapse (Rohsenow, Monti, Rubonis, Sirota, Niaura, Colby, Wunchel & Abrams, 1994; Drummond and Glautier, 1994).

Against this background, Cue Exposure Therapy (CET) has been mentioned as a promising treatment for addiction, since it aims at reducing cue reactivity. During CET, addicts are repeatedly and intensively exposed to individualized drug-related cues, while preventing their habitual response (i.e., drug use). It is assumed that these drug-related cues ultimately loose their predictive value, and cue reactivity such as craving or physiological symptoms is extinguished (Drummond et al., 1995).

A more cognitive viewpoint is that CET may be effective through increasing participant's self-efficacy, i.e., the perceived ability to handle drug-related high-risk situations (Marlatt, 1990).

CET has been applied among alcohol and drug abusers after effectiveness was demonstrated in clients with a phobic anxiety disorder or an obsessive compulsive disorder (Ito, De Araujo, Tess, De Barros-Neto, Asbahr & Marks, 2001; Araujo, Ito & Marks, 1996). Some studies with abstinent addicts have attempted to extinguish cue reactivity by means of Cue Exposure Therapy (Powell, Gray & Bradley, 1993; Dawe, Powell, Richards, Gossop, Marks, Strang & Gray, 1993; Drummond and Glautier, 1994). However, a recent meta-analysis of cue-exposure studies in addicts revealed that the overall effect-size was small and the overall effect of the intervention not significant (Conklin & Tiffany, 2002).

In general, these studies are problematic because they often 1) do not include a (randomised) control treatment, 2) do not provide follow-up information, 3) do not include both physiological and self-report measurements, and 4) generally have a small sample size. For example, only one of the seven cue exposure studies with opiate addicts included a control group and post-treatment follow-up (Dawe et al., 1993). In this study, no significant benefit of cue exposure therapy was found compared to control therapy. However, based on theoretical insights (Conklin & Tiffany, 2002), cue exposure is presumed to have a potential merit if provided under the right circumstances.

The current efficacy study addresses some of the methodological and practical limitations of the earlier studies. This resulted in a study in which we used in-vivo exposure to the smell of heroin vapours, the use of both self-reported and physiological assessments, sufficient sample size, follow-up assessments after three months and the inclusion of a control-treatment.

This study reports on a controlled trial in which abstinent opiate dependent clients were randomised into either a cue exposure treatment group (CET) or a placebo psychotherapy control group (PPT). It is hypothesized that CET will result in larger reductions of both subjective and physiological reactivity than non-active control intervention (PPT).

Furthermore, we hypothesize that cue exposure treatment, through the mechanism of extinguishing drug-related cue reactivity, will reduce (1) early dropout, and (2) relapse. In addition, the current study explores the possible intermediate

effects of (reduced) cue-reactivity (craving, skin conductance) and increased self-efficacy on the relationship between treatment and outcome (drop-out, relapse).

## Methods

### *Participants*

Participants were 127 abstinent heroin dependent clients, admitted to an inpatient drug-free treatment setting of Parnassia Mental Health Institute in The Hague. To be included in the study, the participants had to (a) be heroin dependent (DSM-IV; APA, 1994), (b) have administered heroin primarily through intravenous injection or inhalation, (c) be at least 18 years old, (d) have sufficient understanding of the Dutch language, and (e) have provided written informed consent. Clients with suicidal ideation or psychotic symptoms were excluded from the study.

### *Assessments*

All participants were assessed before treatment (baseline), one day after the last treatment session (post-treatment), and three months after completion of the intervention (follow-up) by a trained research assistant.

Addiction Severity Index (ASI): The ASI is a semi-structured interview assessing baseline characteristics and problems in various domains of life; i.e., alcohol and drug use, physical and mental health, employment, legal problems and social functioning (McLellan, Luborski, Woody, & O'Brien, 1980; Hendriks, Kaplan, Van Limbeek, Geerlings, 1989). The ASI was assessed at baseline and at three-month follow-up.

The Desires for Drug Questionnaire (DDQ): The DDQ is derived from the 14-item Desires for Alcohol Questionnaire (DAQ); (Love, James & Willner, 1998), and adapted for heroin users by Franken, Hendriks and Van den Brink (2002). The DDQ measures three dimensions of current craving: desire and intention to use heroin, negative reinforcement of heroin use, and control of heroin use, with good reliability and concurrent validity (Franken et al., 2002). In this study only the 'desire scale' was used, since it is the most direct indicator of current heroin craving.

The Visual Analog Scale for Craving: The VAS is a 100 mm line on which participants had to rate their subjective experience of current craving for heroin, ranging from "not at all" (0) to "extremely" (100).

Profile Of Mood States (POMS): The POMS is a 32 item self-report questionnaire, measuring instant mood states on five different subscales: depression, anxiety, fatigue, vigour and tension. These subscales have good reliability and construct validity (McNair, Lorr & Droppelman, 1992; Wald & Mellenbergh, 1990).

Self-Efficacy List for Drugs users (SELD): This 22-item instrument, originally based on the scale of drinking habits (Walburg, 1985), was adapted for drug use and was found to be a reliable and valid instrument for measuring self-efficacy in closely defined situations. Self-efficacy for drug users is best described by three dimensions: environmental factors, negative moods, and positive moods (de Weert-van Oene, Breteler, Schippers, Schrijvers, 2000). In the present study the environmental factors scale was used since we found it to be most related to the type of cue exposure treatment performed and therefore the most relevant scale.

Skin Conductance: Skin conductance was measured by a 24-bit digital amplifier (Contact Precision Instruments), using electrodes placed on the fingers of non-dominant hand of the subject. Skin conductance response (SCR) measures phasic responses that reflect the sudden impact of a discrete stimulus, particularly if it has significance for the subject (Hugdahl, 1995). SCR represents the mean number of skin conductance waves observed during a specified time-interval and has been found to be an adequate measure of physiological reactivity in opiate addicts (Hugdahl and Ternes, 1981). Skin conductance data were processed using PSYLAB analysis software (PSYLAB 7, Contact Precision Instruments).

Evaluation scale: Participants were asked to rate how helpful they had perceived the treatment on a scale ranging from 0 (not helpful at all) to 5 (extremely helpful).

*Procedure*

The study was approved by the Medical Ethical Committee, and conducted according to the principles of the Declaration of Helsinki as adopted in Hong Kong (1989).

Clients were successfully detoxified and abstinent for at least two weeks before entering the study. After receiving information and signing informed consent, the baseline measurement was conducted by a trained research assistant. Participants were first exposed to a 5-minute 'neutral' video, depicting a landscape. Subsequently, a cue reactivity-eliciting video was displayed, depicting a heroin user, either smoking or injecting his heroin, depending on the preferred route of heroin-intake of the participant. During the exposure, vaporized heroin was used as an

additional olfactory cue, in order to maximize participant's cue reactivity levels. During both videos, skin conductance responses were measured. Subjective reactivity, i.e., craving and mood states, was assessed immediately after the videos.

Following this baseline assessment, clients were randomised to either the CET condition (N=65) or the placebo-psycho-therapy (PPT) (N=62).

## Treatments

### *Cue Exposure Therapy (CET)*

When randomised to the cue exposure condition (CET), subjects received a protocolized treatment of nine one-hour sessions, which consisted of (in vivo) exposure to highly individualized drug-related stimuli with response prevention. Every session started with a clear rationale of theory behind CET to ascertain that the client was aware of the purpose of therapy. Drug-related stimuli, which were expected to elicit the most craving, were examined by the therapist during the first session and reported in a craving review. In addition to the highly individualized cues, interactions between co-occurring cues were identified as the so-called "cue-clusters" (Drummond, 2000).

If a particular cue only had salience for an individual in a particular context, attempts were made to create this context in the therapy using role playing or by offering multiple cues in a pair wise fashion. We also examined whether in the past certain cues sequentially had caused a relapse. If present, these so-called cue-chains were reproduced during cue exposure sessions. Salient cues often reported by clients were drug paraphernalia such as tin foil, and needles, which were used to mimic the drug-use ritual. Other common cues were, for example, videos of other drug users and neighbourhoods associated with heroin use. Exposure to the sight and smell of actual heroin was supposed to enhance the efficacy of CET since the availability aspect may result in the elicitation of strong conditioned drug-like responses (Drummond et al., 1995). Clients were asked to report their craving for heroin on a scale ranging from '0' (absolutely no craving at all) to '10' (extremely intense craving). Craving was raised as high as possible and during this state of maximized craving, clients were instructed to remain in the situation and stay focused on the cues until extinction took place. The individualized cues were presented to the client in a hierarchic sequence; cue reactivity was first extinguished for relatively 'easy' cues, before the next cue was presented. After each session, possible

remaining craving was diminished by the use of craving-related coping strategies where clients were taught how to handle moments of intense craving and where they learned to reduce this craving with simple behavioural techniques. At the end of the last session an evaluation of therapy took place.

*Placebo-psychotherapy (PPT)*

When randomised into the control condition, subjects received the same amount of one-hour protocolized sessions. This non-specific control treatment was based on relaxation techniques and instructions on how to deal with disturbing emotions and thoughts. The PPT condition was presumed not to have any effect on cue reactivity and was designed around existing therapeutic elements of the drug-free therapeutic community setting. Therefore, PPT can be seen as a control therapy that controls for non-specific factors such as personal attention.

## Data Analysis

Figure 1 describes the flow of participants throughout the study. Of the 127 randomised subjects, 13 subjects terminated the treatment prematurely (CET: n=10; PPT: n=3).

*Cue reactivity*

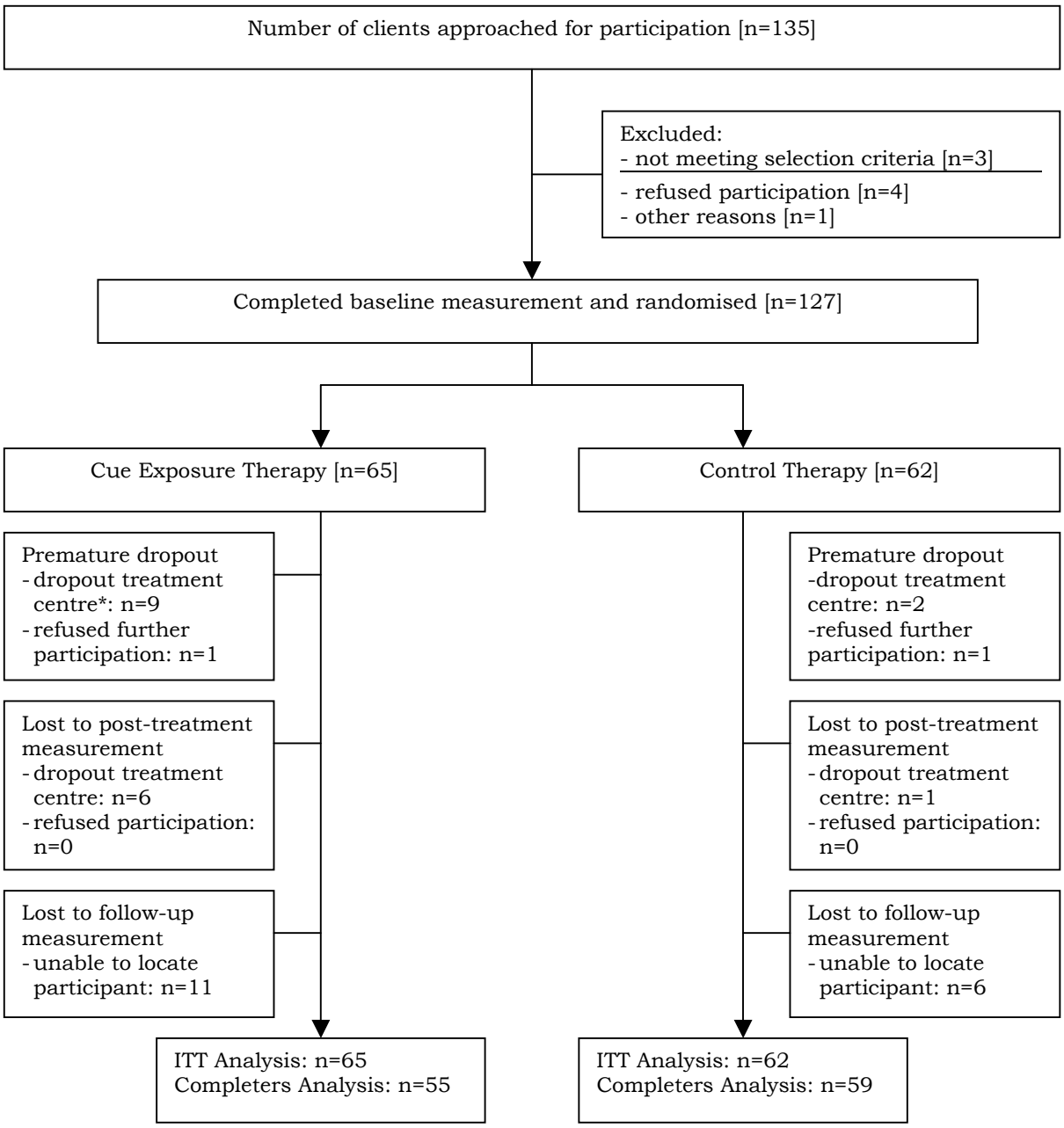
One hundred and twenty subjects completed the post-treatment measurement (CET: n=59; PPT: n=61). In case of relapse, no physiological assessments were conducted. Furthermore, some of the physiological measures were lost due to technical failures. For 91 subjects, complete SCR data were available at post-treatment. Analysis concerning cue reactivity was performed with the available complete datasets. Given the non-normal distribution of the data, Mann-Whitney tests were performed to investigate possible differences in baseline characteristics between the two treatment conditions. A mixed design ANOVA (2 x 2 x 2) was conducted to examine differences in post-treatment cue reactivity (DDQ, VAS, POMS, SCR), with time of measurement (baseline, post-treatment) and stimulus-type (neutral vs. heroin) as repeated measures variables, and treatment condition (CET or PPT) as between subjects' variable. Analyses were performed on the available datasets. Only significant results will be reported. Greenhouse-Geisser test statistics were reported to correct for sphericity.

*Drop-out/relapse*

The dropout/relapse questions were answered in an intention-to-treat analysis, i.e., in all clients randomised (N=127). Subsequently, a 'completers analysis' was applied with all those clients who completed at least seven treatment sessions according to protocol (N=114).

All clients without a three-month follow-up assessment were considered as non-responders, and thus relapsers. This scenario is probably a realistic one since it is known from the literature that most addicts who drop out of treatment, experience a relapse episode shortly afterwards (e.g., Gossop, Green, Phillips, & Bradley, 1989). An independent t-test was used to examine differences in perceived helpfulness of therapy. The relation between treatment condition (CET versus PPT) and treatment response (drop-out, relapse) was examined using logistic regression.

**Figure 1 Flowchart**




* Dropout treatment centre refers to the premature ending in one of both therapeutic settings; clients can voluntarely leave their treatment program or be sent away with regard to violation of house rules, i.e., aggression or substance use.

First, in the logistic regression model, treatment condition was entered, to obtain crude Odds-Ratio's (ORs) on both dependent variables (dropout and relapse). To examine the relative contribution of intermediate variables, we included three additional variables in the regression model; self-reported desire for heroin (DDQ), skin condition responses (SCR) and self-efficacy. For these variables we first calculated the difference between baseline and post-therapy scores and then divided the change scores in clinically relevant sub-groups (no increase/increase/high increase) for self-efficacy scores and (no decrease/decrease/high decrease) for DDQ and SCR scores. These variables were then added to the logistic model and their effect was analysed using a backward stepwise method (Hosmer & Lemeshow, 1989). in order to obtain adjusted ORs . Substantial reductions in the adjusted ORs compared to the crude ORs were interpreted as an indication for the mediating role of the variable under study in the relationship between treatment and outcome (drop-out, relapse).

## Results

### *Sample characteristics*

No differences in baseline characteristics were observed between the subjects in the two groups, except for mean age; CET: 35.1 years vs. 32.1 years in the PPT condition (Mann-Whitney U=1528, *p*=. 019). Overall, participants reported quite severe problems in several domains of life. The study's sample consisted of mostly male subjects (89%) with a low or middle level of education (95%). Most participants were of Dutch/Western nationality (83%). The (cumulative) mean number of regular heroin use was 9.2 years (sd 6.7) with an age of onset of 21.2 years (sd 5.8). Poly-drug use was very common, 91% used cocaine next to heroin. Most participants had already received intensive drug-treatment previously, e.g., 69% was ever in residential treatment, and 64% was ever under methadone maintenance treatment. The main route of administering heroin was "chasing", i.e., smoking (88%); a small group injected heroin (12%). One third of the sample was incarcerated before admission to the residential treatment centre. For those not incarcerated, illegal activities was the major source of income for 23%. Most participants (75%) reported problems of psychological nature, most common problems were depression (24%); anxiety disorder (29%) and impulse control problems; mainly aggression (29%). After

the nine sessions, both groups equally reported they perceived the therapy as helpful as indicated by a Mann-Whitney Test (mean ranks for CET 42.23 vs. 41.77 for PPT, p=.93).

*Cue-reactivity*

Table 1 (first and third column) shows cue reactivity levels as response to neutral and heroin stimuli at baseline ($t^0$) and post-therapy measurements ($t^1$)

*CET and subjective cue-reactivity*

Significant time-effects from baseline to post-therapy measurement were found for self-reported craving on DDQ (F(1, 115) =21.45; *p*=.000), and VAS (F(1, 118) =25.39; *p*=.000). Also, significant cue type effects (from neutral to heroin cue) were found for DDQ (F(1, 118) =108.61; *p*=.000), and VAS (F(1, 115) =29.64; *p*=.000). Furthermore, significant time X cue-type effects were found for DDQ (F(1, 115) =7.73; *p*=.006) and VAS (F(1, 118) =17.87; *p*=.000). Thus, in both groups, self-reported craving for heroin significantly increased after the presentation of a drug-related stimulus, and was significantly decreased for both types of stimuli at post-therapy measurement compared to baseline.

For self-reported mood, as measured by the POMS, significant time effects were found for anger (F(1, 116) =12.44; *p*=.001), depression (F(1, 115) =16.06; *p*=.000), and tension (F(1, 115) =53.02; *p*=.000). Significant effects were found for cue-type: anger F(1, 116) =40.43; *p*=.000, vigour F(1,114) =40.04; *p*=.000 and tension F(1,115) =39.61, *p*=.000. Also significant time X cue-type interaction effects were found: anger F(1, 116) =27.40; *p*=.000, depression F(1, 115) =5.81; *p*=.017, and tension F(1, 115) =16.60; *p*=.000.

Repeated measures analysis revealed no significant three-way interaction of time by stimulus type by treatment condition and thus no significant effect of CET compared to control treatment on self-reported reactivity was found. Both groups showed a similar

decrease from baseline to post-treatment self-reported cue reactivity on heroin-related stimuli on the DDQ, VAS, and POMS.

*Table 1 (first and third column) shows cue reactivity levels as response to neutral and heroin stimuli at baseline ($t^0$) and post-therapy measurements ($t^1$)*

| | Placebo Psycho-Therapy (n= 62) | | | | Cue Exposure Therapy (n=65) | | | |
|---|---|---|---|---|---|---|---|---|
| | $t^o$ (n=62) | | $t^1$ (n=61) | | $t^o$ (n=65) | | $t^1$ (n=59) | |
| | n | h | n | h | n | h | n | h |
| DDQ Desire | 12.0 (6.7) | 16.7 ( 10.2) | 10.2 (6.1) | 12.3 (9.4) | 10.8 (5.8) | 14.1 (8.6) | 9.0 (4.2) | 9.9 (5.8) |
| VAS | 1.0 (1.6) | 3.3 (2.7) | 0.7 (1.2) | 2.2 (2.7) | .7 (1.0) | 2.9 (2.7) | 0.5 (1.0) | 1.6 (2.1) |
| POMS total | | | | | | | | |
| Anger | 2.3 (4.2) | 5.7 (5.9) | 2.0 (3.5) | 3.2 (5.7) | 1.2 (2.2) | 4.9 (6.0) | 1.5 (2.5) | 2.5 (3.9) |
| Depression | 5.2 (6.5) | 7.0 (7.1) | 3.9 (5.5) | 3.7 (5.6) | 3.5 (4.5) | 4.6 (6.0) | 3.0 (3.6) | 2.9 (4.5) |
| Fatigue | 3.5 (4.7) | 4.5 (4.6) | 4.3 (6.0) | 4.2 (5.7) | 2.7 (3.7) | 2.6 (3.7) | 3.0 (4.2) | 2.7 (4.4) |
| Vigour | 9.0 (4.8) | 6.3 (5.2) | 8.6 (4.5) | 7.1 (5.1) | 7.7 (4.4) | 6.6 (5.0) | 8.5 (4.2) | 7.5 (4.3) |
| Tension | 5.0 (4.5) | 8.0 (6.2) | 3.0 (4.0) | 4.2 (5.0) | 4.2 (3.4) | 6.8 (5.4) | 2.6 (2.9) | 3.1 (3.8) |
| Skin conductance response (SCR) | 21.9 (13.3) | 30.6 (12.5) | 15.1 (10.8) | 24.8 (11.8) | 20.9 (12.6) | 30.7 (13.1) | 18.5 (13.3) | 21.0 (11.9) |

### *CET and physiological cue-reactivity*

Concerning physiological cue reactivity, a significant time effect was found for decrease of SCR from baseline to post-therapy measurement ($F(1, 89) = 22.04$; $p = .000$), a significant effect for cue-type ($F(1, 89) = 71.83$; $p = .000$) and a significant time X cue-type interaction effect ($F(1, 89) = 5.78$; $p = .018$).

The only significant three-way interaction of time by stimulus type by treatment condition was found for SCR ($F(1, 89) = 10.65$; $p = .002$) , indicating a significant decrease in skin conductance responses (SCR) in the CET condition but not in the PPT condition at post-therapy measurement.

*Effects of CET on treatment drop-out*

For 3-month dropout status, the analysis of the intention-to treat-sample showed significant differences between groups in favour of the control group. In the CET condition 50.8% of participants had dropped out of long-term, abstinence-orientated treatment, compared to 22.6% in the control treatment within the first three months. The difference of 28% corresponds with an Odds-Ratio of 3.54 and is significant (Wald (1)= 10.37; (95%-CI: 1.64-7.63); $p$ =.001).

When performing the completers analysis, differences between groups remained significant, with an Odds-Ratio of 2.54, Wald (1)=5.03; (95%-CI: 1.12-5.75); $p$ =.03. Dropout percentages were 41.8% in the CET group vs. 22% in the control group.

*Effect of CET on relapse*

In the intention-to-treat sample, significant differences at three-month relapse status were found, again in favour of the control group. In the CET condition, 40.0% of the participants had relapsed into heroin use at least one time, whereas in the control group 12.9% relapsed. This analysis was performed considering all missing data at follow-up as non-responders. The 27% difference corresponds with an Odds-Ratio of .24, which is again significant (Wald (1) = 9.94, 95%-CI: .09 - .58; $p$ = 0.02).

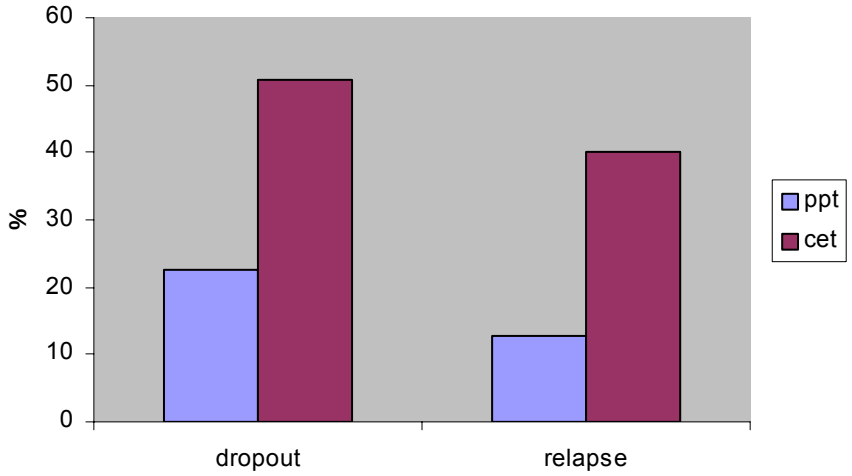
In the completers analysis the difference in relapse between groups remained significant (Odds-Ratio = .26; Wald (1) = 7.70; (95%-CI: .10-.67); $p$ =.01). Relapse rates were 34.5% in the CET group compared to 11.9% in the control group. Both dropout and relapse percentages are depicted in figure 2.

*Intermediate variables: the role of cue reactivity and self-efficacy*

To examine the effect of possible intermediate variables on dropout and relapse, we included three additional variables in the logistic regression model; DDQ-desire, SCR and self-efficacy. In addition, we examined the possible interaction-effects of these variables and treatment condition on outcome (drop-out and relapse).

First, we analysed the effect of the intermediate variables and their interaction with treatment condition on dropout. Performing a backward stepwise method, all variables were excluded from the model. A similar procedure was executed with relapse as the dependent variable. Again, none of the intermediate variables significantly contributed to the logistic models.

. Figure 2 Dropout and relapse rates




## Discussion

Our hypothesis that Cue Exposure Therapy is a potentially effective intervention in reducing dropout and relapse rates in a population of abstinent heroin dependent clients in residential treatment was not confirmed. In fact, we found the opposite effect, significant differences in dropout and relapse at the expense of the experimental group after the intervention. Although skin conductance reactivity was significantly reduced in our experimental group compared to the control group, this was not related to the observed differences at three-month follow-up. These results were highly unexpected and made us re-examine the concept of Cue Exposure Therapy, both on theoretical and clinical grounds.

### *Cue reactivity*

First, from a theoretical point of view, the cue exposure paradigm predicts that both subjective and physiological cue reactivity will be reduced after repeated exposure to drug-related stimuli while preventing a drug use response. However, the present study with abstinent heroin dependent clients produced equivocal results: CET ,- compared to non-active control treatment ,- did reduce physiological reactivity (i.e., skin conductance responses), but not self-reported craving and mood. Significant reductions in craving and mood levels from baseline to post-treatment were observed, but these were independent of treatment condition.

These findings add to the results of various earlier studies, in which CET either produced only partial effects on cue reactivity (i.e., only on autonomic reactivity, (McCusker & Brown, 1995), tension (Drummond and Glautier, 1994) or only for high-cravers (Monti, Rohsenow, Rubonis, Niaura, Sirota, Colby, Goddard & Abrams,1993), or produced no effects on cue reactivity levels at all (Dawe et al., 1993; ;Niaura, Abrams, Shadel, Rohsenow, Monti & Sirota, 1999; Rohsenow, Monti, Rubonis, Gulliver, Colby, Binkhoff, & Abrams, 2001). The present results are in line with an earlier randomised controlled study in abstinent opiate addicts, in which the authors observed a similar decline in subjective craving after both CET and control treatment (Dawe et al., 1993).

Several factors may - at least partially - account for the observed differences in subjective (craving, mood) and objective (SCR) response to CET. First, pre-treatment craving levels may have been low or absent in some participants, which might have created a floor-effect in self-reported craving levels. Secondary post-hoc analyses showed that, indeed, one-third of the subjects did not report clinically relevant craving levels at baseline. However, when excluding this group from the analyses, still no effect could be observed. Second, it might be that the decrease in self-reported craving in the control group partly reflects a tendency to provide the researchers with socially desirable answers whereas the decrease in the CET group may have reflected an actual decrease in self-reported craving. In an earlier study we found that social desirability was negatively correlated with self-reported, but not with physiological reactivity (this thesis, chapter 3). However, when controlling for social desirability, by including this variable as a covariate in the repeated measures analysis, no significant effect of CET compared to control therapy on subjective craving was found.

From a methodological viewpoint, the current findings on cue reactivity stress the importance of including a (randomised) control condition in CET-studies. The overall reductions in subjective craving observed among subjects in both treatment conditions suggest that craving levels would have reduced over time anyway, regardless of the intervention. Earlier findings in non-controlled CET-studies should therefore be interpreted with caution. For example, Powell et al. (1993), who observed a decrease in cue reactivity after only two cue exposure sessions in their non-controlled study, emphasized that "It is not clear whether it is the cue exposure *per se* which promoted the reduction of craving, or whether the change might equally

well be attributed to non-specific factors associated with the treatment sessions, such as "familiarity with the therapist" (Powell et al., 1993).

*Treatment outcome*

Some authors have suggested that autonomic drug-related cue reactivity is an important precursor of relapse, even more so than self-reported craving (Rohsenow, Monti, Abrams, Rubonis, 1992; Rohsenow et al., 2001). However, the current results suggest otherwise. It seems that optimised CET can cause reductions in physiological cue-reactivity in opiate addicts, but this reduced cue-reactivity does not seem to prevent dropout or relapse.

A possible explanation for the unexpected direction of the difference in treatment outcome might be that the CET group, through therapy, obtained higher levels of self- efficacy, which led to overestimation of the ability to handle drug-related situations. Some clients mentioned at follow-up that they had "tested" themselves in drug-situations, which might have exposed them to unnecessary high-risk situations. However, in the current study increased self-efficacy as a result of therapy could not explain the differences in dropout and relapse at follow up.

If not the changes in cue reactivity or self-efficacy, another mechanism must have been responsible for the unexpected direction of the differences in dropout and relapse between the two groups. It could be that the placebo-psychotherapy was unexpectedly effective. The PPT, however, was restricted to some minor extension of already existing treatment modules in the drug-free therapeutic community where the clients were living during the study. The supportive character of the therapy, where the role of the therapist consisted mostly of listening, showing empathy and providing a good therapeutic relationship, may have had some non-specific effects. If this is the case, individual attention from a therapist for clients admitted in a group setting may have been more important than we originally thought. However, clients did not perceive the PPT as more helpful compared to CET, both therapies were equally evaluated as 'very helpful'.

A third explanation could be that CET was too confronting and therefore had a negative effect on dropout and relapse. The current study shows that more CET than PPT clients ended the treatment prematurely (10 of 65 in CET (15%) versus 3 of 62 (5%) in PPT).

A fourth explanation of the current results is the possibility that CET extincts only responses to specific stimuli under specific circumstances and therefore might have

had unintended effects (Robinson and Berridge, 1993). The current results are in line with the incentive-sensitisation theory of Robinson and Berridge (1993) which states that through persistent drug use, long-lasting neuroadaptations are produced, which make brain reward systems become highly sensitised to drugs and drug-related stimuli. It is hypothesised that after CET, while some learned, conditioned stimuli-associations can be extinguished, neuroadaptations underlying sensitisation persists and are resistant to extinction. It could very well be that through CET only 'superficial' cue reactivity has been extinguished while 'triggering' the underlying sensitive neural systems, and hereby creating a vulnerability to relapse into drug-use. Also, Marlatt (1990), for example warns for a 'paradoxical increased sensitisation effect' as a result of CET; after the drug user experiences a first lapse. Assuming that CET extinguishes conditioned compensatory responses (Siegel, 1983) CET might leave the drug user unprepared to high-risk situations and subsequently to the unconditioned drug effects (Marlatt, 1990). Through CET the person then has become more vulnerable to relapse after a first lapse. This first lapse is something that CET tries to prevent. However, with the results from the present study we cannot exclude the possibility that CET in the current form can also create a certain vulnerability or hypersensitivity which may unintentionally facilitate a first lapse.

With the currently available information we are unable to empirically explain the unexpected differences in relapse. This, however, should not refrain us from a warning against the potential harmful consequences of CET under certain conditions.

### *Limitations of the study*

Applications in the field of brain imaging, such as PET or fMRI (Hommer, 1999), may have provided us with more direct and accurate indicators of autonomic reactivity, and are likely to contribute significantly to our understanding of the relation between cue reactivity and relapse.

As mentioned before, one third of the subjects did not report cue reactivity to the drug-related stimulus at baseline. Perhaps, higher cue reactivity levels could have been elicited through offering more realistic stimuli, such as in-vivo exposure to high-risk situations. Also, developments in the area of virtual reality may offer new possibilities in cue reactivity research (Kuntze, Stoermer, Mager, Roessler, Mueller-Spahn, Bullinger, 2001).

Retrospectively we are unable to test which of the explanations or a combination of these, could have led up to the failure of CET being an effective therapy for this

population. Perhaps CET still has the potential of becoming an effective treatment under different circumstances, i.e., in another population or another treatment setting. It has been shown that through CET physiological reactivity can be extinguished but that this is not associated with a positive treatment outcome. It might be that we provided CET in the inappropriate time-span, or should have provided booster-sessions throughout the follow up period. A more extensive follow-up period would have given us more information concerning the natural course of cue reactivity in abstinent addicts. Another possibility could be that CET was given too early after detoxification when clients are still quite vulnerable. Furthermore, CET was given in the clinical setting without actually accompanying clients into their natural environment, which might have prevented generalization from taking place. In addition, most of our participants were poly-drug users, i.e., used cocaine next to heroin and received a treatment directed mainly on heroin addiction.

We intentionally did not apply coping strategies during CET, but only after the exposure sessions, in order to examine the "pure" effect of the exposure and subsequently extinction. Other studies among alcoholics have provided CET in combination with intensive coping skills training and found clearly better results concerning treatment outcome among abstinent addicts (Monti et al., 1993; Rohsenow et al., 2001; Monti, Rohsenow, Swift, Gulliver, Colby, Mueller, Brown, Gordon, Abrams, Niaura & Asher, 2001). Monti et al (1993) found an effect of CET with coping skills, not during the first three-month follow-up , but only during a second three-month follow up. The authors conclude that the effect is probably explained by the fact that participants applied coping strategies after a first lapse, but that the extinction component in the therapy did not contribute to the effect. The present results raise the very important question whether CET without coping skills training might be detrimental instead of being a beneficial treatment. As a consequence, CET trials and interventions should only be performed if clients can be simultaneously offered additional tools to learn how to 'cope' with drug-related high-risk situations rather than merely exposing them to these risks.

Until further research provides us with more clarity concerning the mechanisms underlying CET, we should be careful in providing clients with this intervention, at least without simultaneously providing coping skills training. In conclusion, this is the first randomised clinical trial that showed that CET alone might increase dropout and relapse in a population of abstinent heroin dependent clients in residential treatment and might thus be harmful rather than beneficial.

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# Chapter 6

# Attentional bias predicts heroin dependence following treatment

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## Abstract

Previous studies have shown that abstinent heroin addicts exhibit an attentional bias to heroin-related stimuli. It has been suggested that attentional bias may represent a vulnerability to relapse into drug use. In the present study, the predictive value of attentional bias on relapse was examined in a population of abstinent heroin addicts. Further, the effect of Cue Exposure Therapy (CET) on attentional bias was studied. Participants were randomly assigned to receive nine sessions of CET or placebo psychotherapy. They completed the emotional Stroop task both before and after completing treatment. Attentional bias was reduced in both groups after therapy, independent of treatment condition. Pre-treatment attentional bias predicted relapse at three-month follow up, even when controlling for self-reported cravings at the test session. In sum, attentional bias may tap an important component of drug dependence, but it is not reduced by CET.

# Introduction

Research has repeatedly demonstrated that cognitive functioning can be influenced by emotional disturbance or pre-occupation with concern-related stimuli (Williams, Mathews, & MacLeod, 1996). For example, participants with spider phobia allocate more attention to spider-related stimuli than to neutral stimuli. This phenomenon is called attentional bias. The emotional Stroop task is often used to measure attentional bias. In this task, participants have to name the colours in which words are printed (Williams et al., 1996). Individuals with emotional disorders tend to take a longer time to name the colours of the words that reflect their emotional state or concerns compared to neutral words. Attentional bias to threat-related words has been shown for various types of psychopathology, such as phobias, depression, post-traumatic stress disorder and obsessive-compulsive disorder (Williams et al., 1996). Therefore, attentional bias for disorder-related words may be an indication for the presence of psychopathology (Williams et al., 1996).

Many recent studies have used the emotional Stroop task to examine attentional biases in the addictions. In addiction Stroop tasks, the presented stimuli may be incentive stimuli (i.e., associated with “approach” behaviour) rather than threatening stimuli (i.e., associated with “avoidance”). Attentional bias has been shown for many drug-types including alcohol (Kramer & Goldman, 2003), nicotine (Gross, Jarvik, & Rosenblatt, 1993; Bradley, Mogg, Wright & Field, 2003), cannabis (Field, Mogg & Bradley, 2004) and cocaine (Rosse, Johri, Kendrick, Hess, Alim, Miller & Deutsch, 1997). Moreover, an attentional bias for heroin cues was found in abstinent heroin addicts, but not control participants (Franken, Kroon, Wiers, & Jansen, 2000). Finally, opiate abusers on methadone exhibited an attentional bias for drug-related stimuli on a visual dot probe task (Lubman, Peters, Mogg, Bradley, & Deakin, 2000).

It has been argued that attentional bias is not simply a by-product of an emotional disorder but also contributes to its maintenance (Williams et al., 1996). For example, when drug-related stimuli grab the attention of a drug user, they may evoke conditioned responses, such as craving, that can increase the risk for relapse (Drummond, Tiffany, Glautier & Remington, 1995; Lubman et al., 2000). In their incentive-sensitisation theory of addiction, Robinson and Berridge (1993) argue that through the process of repeated drug-intake, addicts attribute incentive salience to drug-related stimuli. Stimuli with excessive incentive salience become excessively

“wanted”, thereby maintaining addictive behaviour. In addition, Franken (2003) states that attentional bias is a cognitive intermediate between drug-related stimuli and relapse. This is partly due to the fact that enhanced (autonomic) signalling of drug cues leaves fewer resources for the addict to apply appropriate coping strategies.

More empirically, the importance of attentional bias was demonstrated in a recent study which reported that smokers with high attentional bias towards tobacco-related words (on an emotional Stroop task) were significantly more likely to relapse in the short-term compared to smokers with less attentional bias (Waters, Shiffman, Sayette, et al., 2003; see also Cox, Hogan, Kristian, & Race, 2002). Thus, it seems important to find interventions that reduce attentional bias. Importantly, studies have demonstrated that attentional bias to threatening stimuli can indeed be modified by behavioural treatment. For example, decreases in attentional bias after therapy have been documented among anxious participants (Mathews, Mogg, Kentish & Eysenck, 1995) and among individuals with phobic disorders (Lavy, van den Hout & Arntz, 1993).

In order to further evaluate the clinical relevance of attentional bias, we examined whether attentional bias is a predictor of relapse to heroin use. Also, associations between attentional bias and self-reported craving were examined.

The present study is part of a larger randomised controlled trial examining the effects of CET on treatment outcome for heroin addiction (Marissen, Franken, Blanken, van den Brink & Hendriks, submitted, 2004). It has been proposed that responses to drug cues can be reduced using Cue Exposure Therapy (CET), during which addicts are exposed to drug-related stimuli while being prevented from making any response (Powell, Gray, & Bradley, 1993; Franken, de Haan, van der Meer, Haffmans & Hendriks, 1999). One goal of the present study is to examine whether CET - by reducing cue reactivity - can reduce attentional bias to heroin-related cues among abstinent heroin addicts. Assuming that attentional bias reflects attentional responses to drug-related stimuli, and is therefore a component of cue reactivity, we hypothesized that CET would reduce attentional bias towards heroin-related stimuli compared to a placebo psychotherapy.

# Method

## *Participants*

Participants were abstinent heroin addicts, who, after detoxification, were admitted to an in-patient drug-free therapeutic centre in The Hague, the Netherlands. Participants were derived from the randomised clinical trial examining the effects of CET on treatment of heroin addiction. All participants met DSM-IV criteria for heroin dependence (APA, 1994) and were abstinent from any psychoactive substance for at least two weeks. Participants who were psychotic, suicidal or colour blind were excluded from the study. The participants were predominantly male (89%) and averaged 34.0 years of age. Most participants were of Dutch nationality (85%) and had a low or middle level of education (90%). The average age of onset of regular heroin use was 21.4 years, and the participants had regularly used heroin on average for 9.3 years. Most participants were poly-drug users (90% used cocaine in addition to heroin). One third of participants were incarcerated before admission to residential treatment. Most participants reported psychological problems at baseline (75%). Details can be found in Marissen et al., submitted 2004.

## *Procedure*

After the participants gave written informed consent, a baseline assessment was conducted and the participants completed the emotional Stroop task (the pre-treatment test), which was administered individually. Following this task, participants were randomly assigned to either the CET condition or a control condition wherein participants received placebo psychotherapy (PPT). Three weeks later, after completing nine treatment sessions (of CET or PPT), participants completed the Stroop task a second time (the post-treatment test). All participants were abstinent from drug use when completing the Stroop task.

## *Treatment*

During CET, participants were exposed to individualized drug-related cues and were prevented from making their habitual response, i.e., drug use. Cues were chosen that would elicit the greatest cue reactivity in participants. Common cues were drug-related paraphernalia, videos of drug users or drug-related neighbourhoods, or role-plays with the therapist to induce drug-related memories or moods. During the exposure, participants were instructed to remain in the situation

and experience their craving until extinction occurred. Reactivity towards these drug-related stimuli diminished over the nine 1-hr sessions.

During placebo-psychotherapy, participants also received nine 1-hr treatment sessions, to control for non-specific therapy factors such as individual attention from a therapist. During the placebo-psychotherapy sessions, topics such as relaxation and emotion-regulation were discussed. (For a detailed description of treatment methods see Marissen et al., submitted, 2004).

## Measures

### *The Emotional Stroop Task.*

To measure attentional bias to drug-related stimuli, participants performed a computerized Stroop task in which they where asked to name the colours of words appearing on a computer screen (described in Franken et al., 2000). Ten heroin-related words (Dutch equivalent of score, flash, smack, dope, dealer, junk, shot, ball, heroin, inhale) and ten neutral words (Dutch equivalent of pilot, ticket, crosswalk, train, vehicle, bike, scooter, trolley, asphalt, gasoline) were used. The neutral words and heroin words were matched for length and number of syllables. The words were presented to the subjects in 13 mm uppercase letters in the colours green, yellow, blue or red. Words were presented in a different random order for each participant, under the constraints that a specific word category (heroin or neutral) was not presented more than four consecutive times, and that the same colour was not presented more than twice in a row. Each word was presented five times in different colours resulting in a total of 100 trials (50 neutral, 50 heroin). A word was presented on the screen and remained there until a response or for a maximum of 3000 ms. The participants were instructed to colour-name the word as quickly as possible, and there was a 1000 ms inter-trial interval. Reaction time was measured in milliseconds (ms) from the moment of stimulus presentation to the verbal response. The experiment was programmed in EXPE- language (Pallier, Dupoux, & Jeannin, 1997) and was run on an IBM- P-100 PC attached to an IBM colour monitor.

### *Scoring.*

Following Franken et al. (2000), reaction times less than 200 ms were discarded, and trials on which the participants failed to respond within 3000 ms were considered missing data. We constructed two measures of attentional bias. First, we computed

the difference score between the mean reaction times on heroin words minus the mean reaction times on neutral words (the Stroop effect). Second, some studies have reported that drug users are slower to respond to words that follow drug-related words than neutral words (Waters, Sayette, & Wertz, 2003; Waters, Sayette, Franken, & Schwartz, in press), an effect that may capture the difficulty disengaging attention from drug-related stimuli over time. Thus, we also computed a difference score between the mean reaction times on trials following heroin words minus mean reaction times on trials following neutral words (termed the carry-over effect).

*Self-reported craving.*

Self-reported craving for heroin was assessed using the Desires for Drug Questionnaire (DDQ), an instrument which measures instant or current heroin craving. The instrument is a translation of the Desires for Alcohol Questionnaire (DAQ) (Love, James & Wilner, 1998) and adapted for heroin use (Franken, Hendriks & van den Brink, 2002). For this study we used one out of the three scales of the instrument, the "desire and intention" scale, which measures current heroin craving most directly (e.g., "My desire for heroin now seems overwhelming"). DDQ desire scores were first assessed after participants watched a neutral videotape (consisting of landscape views). Subsequently the scores were assessed after participants watched a cue-eliciting videotape, which showed a heroin user either inhaling or injecting heroin (matched to the preferred route of heroin intake of each participant). In an attempt to maximize craving levels we added an olfactory cue; 8 mg. of heroin was vaporized in the room during the heroin video.

## Data Analysis

Stroop data were available from 110 participants from the pre-treatment assessment, and 106 participants from the post-treatment assessment[1]. Ninety-five participants provided data from both the pre-treatment and post-treatment assessments.

We used logistic regression to examine the relationship between Stroop and carry-over effects and relapse at follow-up (defined as "at least one time heroin use

[1] [1]In total 130 participants were enrolled in the study, and completed the pre-treatment assessment. Unfortunately, a computer used to run the Stroop task was stolen, meaning that some data were lost.

within three months after post-treatment measurement"). The Stroop effect was defined as the mean reaction times on heroin targets minus mean reaction times on neutral targets, and the carry-over effect was defined as the mean reaction times on trials following heroin words minus mean reaction times on trials following neutral words. Participants lost to follow-up (n = 9) were considered to have relapsed. This criterion was applied because it is known that dropouts from residential treatment often relapse to drug use soon afterwards (Gossop, Green, Phillips, & Bradley, 1987; Gossop, Stewart, Browne, & Marsden, 2002). Stroop and carry-over effects were tested in separate models. In all logistic regression analyses, treatment condition was included as a covariate. These analyses included the 110 participants who contributed data from the pre-treatment assessment, and the 106 participants who contributed data from the post-treatment assessment. Stroop and carry-over effects were divided by 100 ms to facilitate interpretation of the Odds Ratios. Follow-up analyses used ANOVA to test whether reaction times on different conditions differed by relapse group (abstainers vs. relapsers); treatment condition was included as an independent variable in these models.

To test the effects of time (pre-treatment vs. post-treatment) and treatment condition (CET vs. placebo) on reaction times on target words (neutral vs. heroin) as a function of the word before (neutral vs. heroin), we used repeated measures ANOVA. This analysis used data from the 95 participants who had data at both the pre-treatment and post-treatment assessments. Finally, we used Pearson's r to assess the correlations between Stroop and carry-over effects and self-reported craving measures.

## Results

### *Prediction of Relapse*

Of the 110 participants who had Stroop data from the pre-treatment assessment, 84 reported maintaining abstinence at follow-up (abstainers), and 26 were considered to have relapsed (relapsers). Figure 1 shows the mean reaction times for abstainers and relapsers on N-N, H-N, N-H, and H-H trials. Figure 1 indicates that relapsers responded 69 ms more slowly on H-H trials than N-N trials, whereas abstainers were only 27 ms slower to respond on H-H trials than N-N trials. The Stroop effect (i.e., difference in response time on N-H, H-H trials vs. H-N, N-N trials) predicted relapse using logistic regression (OR = 2.23, C.I. = 1.06, 4.86, $p < .05$). In

this model, the effect of treatment condition was also significant (OR = 0.24, C.I. = 0.08, 0.66, p < .01), indicating that participants treated with CET were at a significantly elevated risk of relapse compared to placebo participants. The carry-over effect (i.e., difference in response time on H-N, H-H trials vs. N-H, N-N trials) also predicted relapse (OR = 3.89, C.I. = 1.05, 14.4, p < .05); in this model, the effect of treatment was also significant (p < .01). As suggested by Figure 1, relapsers showed significant carry-over effects (repeated measures ANOVA, F (1,24) = 7.81, p < .05) whereas abstainers did not (F (1, 82) = 0.23, p = .63).

Of the 106 participants who had Stroop data from the post-treatment assessment, 85 reported maintaining abstinence at follow-up, and 21 were considered to have relapsed. The mean reaction times (in ms) on the N-N, H-N, N-H, H-H conditions were 698.6 (SD = 114), 720.2 (SD = 132), 732.6 (SD = 137), 719.4 (SD = 140), and 693.1 (SD = 113), 699.3 (SD = 120), 711.9 (SD = 121), 711.6 (SD = 114) for the relapsers and abstainers respectively. At the post-treatment assessment, neither the Stroop effect (OR = 1.18, C.I. = 0.37, 3.81, ns) nor the carry-over effect (OR = 0.88, C.I. = 0.25, 3.10, ns) predicted relapse.

*Effects of Treatment Condition on Stroop performance*

Table 1 reports summary statistics on the Stroop task by treatment condition for those participants who completed the Stroop task both at pre-treatment and post-treatment. Mean reaction times are shown for four conditions: neutral words preceded by neutral words (N-N), neutral words preceded by heroin words (H-N), heroin words preceded by neutral words (N-H), and heroin words preceded by heroin words (H-H). A 2 x 2 X 2 X 2 (Time by Treatment by Target by Before) repeated measures ANOVA was conducted on the reaction time data. As expected, there was a large significant effect of Target (F(1, 93) = 30.5, p < .01), indicating that participants were slower to respond on heroin targets than neutral targets (the Stroop effect). There was also a significant Time by Target interaction (F(1, 93) = 4.26, p < .05), indicating that the effect of Target (the Stroop effect) was significantly larger in the pre-treatment test (28.3 ms) than the post-treatment test (14.1 ms). There was a marginally significant effect of Before (F(1, 93) = 3.81, p = .05), indicating that participants were slightly slower to respond to words appearing after heroin targets than words appearing after neutral targets (the carry-over effect). Most importantly, there were no significant effects involving Treatment condition (all ps > .05), indicating that Treatment condition did not moderate Stroop or carry-over effects

(e.g., no Time by Treatment by Target interaction). The only other significant effect was a main effect of Time ($F(1, 93) = 4.89$, $p < .05$), indicating that participants were generally faster to respond on the post-treatment test than the pre-treatment test.

Table 1. RTs as a function of Time of Test and Treatment Condition

| | **Pre-Treatment** | | | | **Post-Treatment** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Placebo** | | **Cue Exposure** | | **Placebo** | | **Cue Exposure** | |
| ***Word Before*** | **N Targets** | **H Targets** | **N Targets** | **H Targets** | **N Targets** | **H Targets** | **N Targets** | **H Targets** |
| ***N*** | **709.8 (124)** | **746.7 (152)** | **706.0 (120)** | **730.3 (136)** | **705.4 (118)** | **723.2 (120)** | **680.9 (100)** | **700.7 (116)** |
| ***H*** | **715.1 (122)** | **745.0 (150)** | **718.4 (122)** | **739.4 (146)** | **708.3 (124)** | **720.3 (114)** | **698.8 (118)** | **705.3 (124)** |

Note: RTs on Neutral and Heroin targets as a function of the word before for Placebo (n = 50) and Cue Exposure (n = 45) participants. Data shown are means (1 SD). Key: N = Neutral, H = Heroin.

### *Associations with Craving at Time-of-Test*

At the pre-treatment session, the mean craving on the neutral video (Craving-N) was 11.4 (SD = 6.26, range 7 - 37), the mean craving on the heroin video (Craving-H) was 15.4 (SD = 9.47, range 7 - 46), and the mean craving cue reactivity score (Craving-H minus Craving-N, Craving-CR) was 4.02 (SD = 8.46, range -30 to 30). The Stroop effect was significantly correlated with Craving-H ($r = .23$, $p < .05$) and Craving-CR ($r = .19$, $p < .05$). Importantly, the Stroop effect continued to predict relapse when controlling for Craving-H (OR = 2.68, C.I. = 1.12, 6.37, $p < .05$) and Craving-CR (OR = 2.39, C.I. = 1.06, 5.36, $p < .05$). In these models, neither Craving-H nor Craving-CR predicted relapse (ps > .20). Unexpectedly, the carry-over effect was significantly negatively correlated with Craving-H ($r = -.21$, $p < .05$) and Craving-CR ($r = -.19$, $p < .05$). The carry-over effect continued to predict relapse when controlling for Craving-H (OR = 3.81, C.I. = 1.02, 14.3, $p < .05$) and Craving-CR (OR = 3.93, C.I. = 1.06, 14.6, $p < .05$). In these models, neither Craving-H nor Craving-CR predicted relapse (ps > .80).

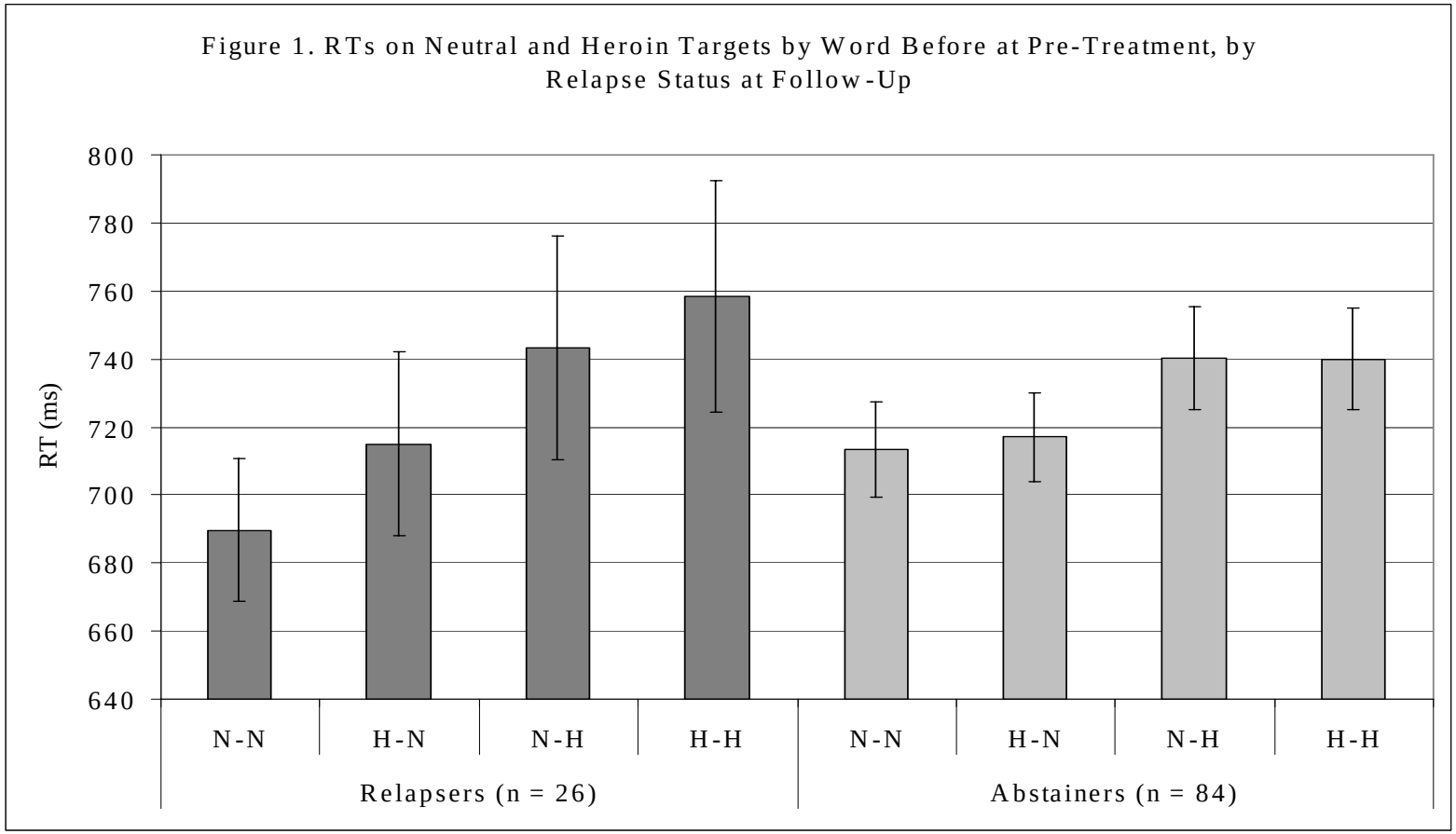


***Figure 1.*** **RTs on Neutral and Heroin Targets by Word Before at Pre-Treatment, by Relapse Status at Follow-Up. Key: Data shown are means (1 SE). N-N = Neutral target preceded by Neutral word; H-N = Neutral target preceded by Heroin word; N-H = Heroin target preceded by Neutral word; H-H = Heroin target preceded by Heroin word.**

## Discussion

The need to reduce attentional bias to drug-related stimuli becomes clear when there is a link between attentional bias and relapse into drug use. The present study provided some support for the clinical relevance of attentional bias. Specifically, individuals who exhibited greater Stroop effects on the pre-treatment assessment were at greater risk for a subsequent relapse. Interestingly, individuals who exhibited greater carry-over effects (slower responses on trials after heroin words) were also at greater risk for relapse, providing further support that attentional responses to drug cues are related to relapse. Furthermore, the Stroop and carry-over effects continued to predict relapse when controlling for self-reported craving measures, thereby confirming that there is information in the attentional bias measure incremental to that gained from self-reported craving. This study is the first to demonstrate an association between attentional bias and relapse in heroin addition, and adds to two previous studies in the addictions literature that have demonstrated associations between attentional bias and relapse (Waters et al., 2003; Cox et al., 2002).

However, in contrast to the positive associations observed at the pre-treatment assessment, there was no evidence that attentional bias at the post-treatment assessment was associated with relapse risk. The meaning of this null finding is unclear. Perhaps attentional bias at post-measurement reflects repeated measurements effects and is therefore not a good predictor of relapse. For example, participants may not be “surprised” by the drug-related stimuli on the second assessment, which may reduce the attention-grabbing properties of these stimuli.

A main finding of the study was that - among a population of abstinent heroin addicts in residential treatment - CET did not reduce attentional bias to heroin-related words more than control therapy. This null effect contrasts with an earlier analysis in which we did observe a significant effect of CET on cue-induced skin conductance reactivity compared to control therapy, confirming the treatment integrity and possible effectiveness of CET (Marissen, Franken, Blanken, van den Brink & Hendriks, submitted, 2004). Thus, CET can reduce physiological reactivity, but not attentional bias, both mechanisms are characterized as not being under direct conscious control of the participant.

However, it is important to note that attentional bias (specifically, the Stroop effect) was significantly reduced between the pre-treatment and post-treatment tests (Time by

Target interaction), independent of treatment condition (no Time by Treatment by Target interaction). Thus, we cannot rule out the possibility that both CET and the control therapy successfully reduced attentional bias, presumably through different mechanisms. However, other explanations are also possible. The decrease in attentional bias might simply reflect the passage of time, as participants recover from acute withdrawal associated with abstinence from heroin. Alternatively, the decrease in attentional bias may reflect effects of repeated measurements. or else participants may get adopt strategies that improves their ability to over-ride the disruptive effect of the heroin-related words. In addition, the heroin cues (the words) are not reinforced (by drug taking) during or after the first assessment. Thus - for both treatment groups - responses on the second assessment might be influenced by extinction processes specific to the heroin-related stimuli in the Stroop task.

If the null effect of CET on attentional bias is taken at face value, it suggests that attentional bias for desirable stimuli, associated with "wanting", is more difficult to extinguish through behavioural treatment than attentional bias for undesirable stimuli, associated with "avoiding". For example, it has been shown that attentional bias for anxiety-related stimuli can be reduced through cognitive behavioural therapy using exposure techniques (Watts, McKenna, Sharrock & Trezise, 1986; Lavy et al., 1993; Mathews et al., 1995). In contrast, studies which attempted to reduce attentional bias for food-related stimuli among bulimic patients through CET have reported less optimistic results (Cooper & Fairburn, 1994; Carter, Bulik, McIntosh & Joyce, 2000). Comparable to the findings in the present study, attentional bias to appetitive stimuli was reduced after therapy, independent of type of treatment.

The possibility that reactivity to appetitive stimuli is less sensitive to extinction calls for a revision of the expected utility of CET in the addiction field. This line of reasoning is in agreement with what is known from cue exposure research: CET has good, clear results in treating anxiety-related disorders, and much more ambivalent results in the treatment of addictive behaviours (Conklin & Tiffany, 2002; Marissen et al., submitted, 2004). Indeed, the unexpected negative effect of CET on treatment outcome we found in our study substantiates this (for a more detailed description of the effect of CET on treatment outcome, see Marissen et al., submitted 2004).

The study had some limitations. There was no biochemical verification of abstinence (such as measures of metabolites in urine samples), and thus all abstinence data were based on self-reports. However, most participants were in residential treatment when completing the Stroop task which minimizes the chance that participants were using

drugs during the treatment phase of the study. As noted earlier, all participants performed the cue reactivity task (exposure to the heroin video) before completing the Stroop task. Strictly speaking, our results speak only to Stroop effects observed after the completion of the cue reactivity task, which was craving-inducing. We cannot be certain that the results will generalize to other testing conditions.

In summary, while it has been shown that attentional bias to drug-related cues is present among abstinent heroin users, this is the first study that has demonstrated an association between attentional bias and clinical outcome in this population. This is also the first study to examine the effect of CET in reducing attentional bias for heroin-related stimuli among dependent heroin users. The fact that we found no effect of CET on attentional bias suggests that CET might be less able to extinguish “approach-related” stimuli compared to “avoidance-related” stimuli. In sum, attentional bias may tap an important component of dependence, but it is not reduced by CET. Further research is required to devise treatments that effectively reduce attentional responses to drug cues.

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## Author Note

This work was supported by a grant (#9604-4) from the Netherlands Organization for Scientific Research (NWO / ZonMw) to Maries Marissen.

The authors wish to thank the clients and staff members of therapeutic treatment center Emiliehoeve and Triple-Ex.

# PART IV: CONCLUSIONS AND RECOMMENDATIONS

# Chapter 7

## "Cue Exposure Therapy as a practical treatment for addictive disorders: Why do we keep trying?".

More than one decade ago, based on a symposium on "Cue Exposure in the Addictive Behaviors", Heather and Bradley (1990) craving scientists in the addiction field to put into practice what conditioning theory has provided us since 1948 when Wikler first recognized the importance of classical conditioning in drug abuse. They wondered why Cue Exposure Therapy (CET), which has a clear theoretical base and has become the treatment of choice for several anxiety disorders (Otto, Safren & Pollack, 2004), does not generalize to the addiction field. The title of their article was "Cue Exposure as a practical treatment for addictive disorders: Why are we waiting?" (Heather & Bradley, 1990). Since then, several attempts have been made to put cue exposure theory into practice and a number of randomised clinical trials have been performed to study the effects of cue exposure therapy. Abstinence-oriented cue exposure therapy studies have been conducted with alcoholics (Monti, Rohsenow, Rubonis, Niaura, Sirota, Colby, Goddard & Abrams, 1993; Drummond & Glautier, 1994; McCusker & Brown, 1995; Sitharthan, Sitharthan, Hough & Kavanagh, 1997; Monti, Rohsenow, Swift, Gulliver, Colby, Mueller, Brown, Gordon, Abrams, Niaura & Asher, 2001; Rohsenow, Monti, Rubonis, Gulliver, Colby, Binkhoff & Abrams, 2001), drug addicts (Kasvikis, Bradley, Powell, Marks & Gray, 1991; Powell, Gray & Bradley, 1993; Dawe, Powell, Richards, Gossop, Marks, Strang & Gray, 1993) and smokers Niaura, Abrams, Shadel, Rohsenow, Monti & Sirota, 1999). Overall, the effect sizes of these cue exposure treatment studies were small and generally not significant (Conklin & Tiffany, 2002).

In the present thesis, the effectiveness of Cue Exposure Therapy was studied in the context of a randomised controlled trial. Participants were diagnosed as heroin dependent, admitted to residential group treatment and currently abstinent of drug use. In the study, we have tried to optimise CET through the presence of actual heroin and its typical odour during exposure sessions and by extinguishing both internal (e.g., mood states) and external cues (e.g., paraphernalia).

We included a placebo treatment (placebo-psychotherapy) to control for a-specific treatment factors such as individual attention from a therapist. We assessed self-

reported cue reactivity (mood, craving), physiological reactivity (skin conductance responses), self-efficacy and attentional bias at baseline, post-treatment and at three-month follow up.

Our main results are outlined in figure 1. We found no effect of CET on self-reported reactivity, i.e., mood, craving, or self-efficacy. In addition, CET had no influence on participant's attentional bias measured by a stroop-task. We did find an effect of CET on skin conductance responses to a heroin-related video, compared to placebo-psychotherapy. This indicates the effectiveness of CET in at least extinguishing physiological cue reactivity. However, the most striking findings of this study were the significant higher drop-out and relapse rates among participants who received CET compared to the placebo-psychotherapy. Therefore, we have stated (this thesis chapter 5) that CET might have detrimental effects in this particular population. This is the first randomised controlled CET trial which, instead of a moderate or no effect, found a negative effect. This might have implications for Cue Exposure Therapy as an intervention in addiction care, both on theoretical as well as clinical grounds. Without the illusion of giving exclusive explanations for the present findings (for a more detailed discussion of these findings see this thesis chapter 5), the main results of this thesis will be discussed in the light of what we know after half a century of research within the cue exposure paradigm.

## Theoretical implications

The theoretical model behind CET predicts that addicts will experience both subjective and physiological cue reactivity when they are exposed to drug-related stimuli, as a result of classical conditioning. By repeatedly associating these drug-related stimuli with a non-habitual response, i.e., not using the drug but simply waiting for the cue reactivity to reduce or extinguish, these stimuli will no longer be associated with the former response, i.e., drug use. Therefore, the drug-related stimuli loose their predictive capacities and eventually their impact, cue reactivity will be diminished. Since cue reactivity is often presumed to be a predictor of relapse (Heather, Stallard & Tebbut, 1991; Rohsenow, Monti, Rubonis, Sirota, Niaura, Colby, Wunchel & Abrams, 1994), extinction of cue reactivity is assumed to make clients less vulnerable and should lead to less dropout and a reduction in relapse into drug use.

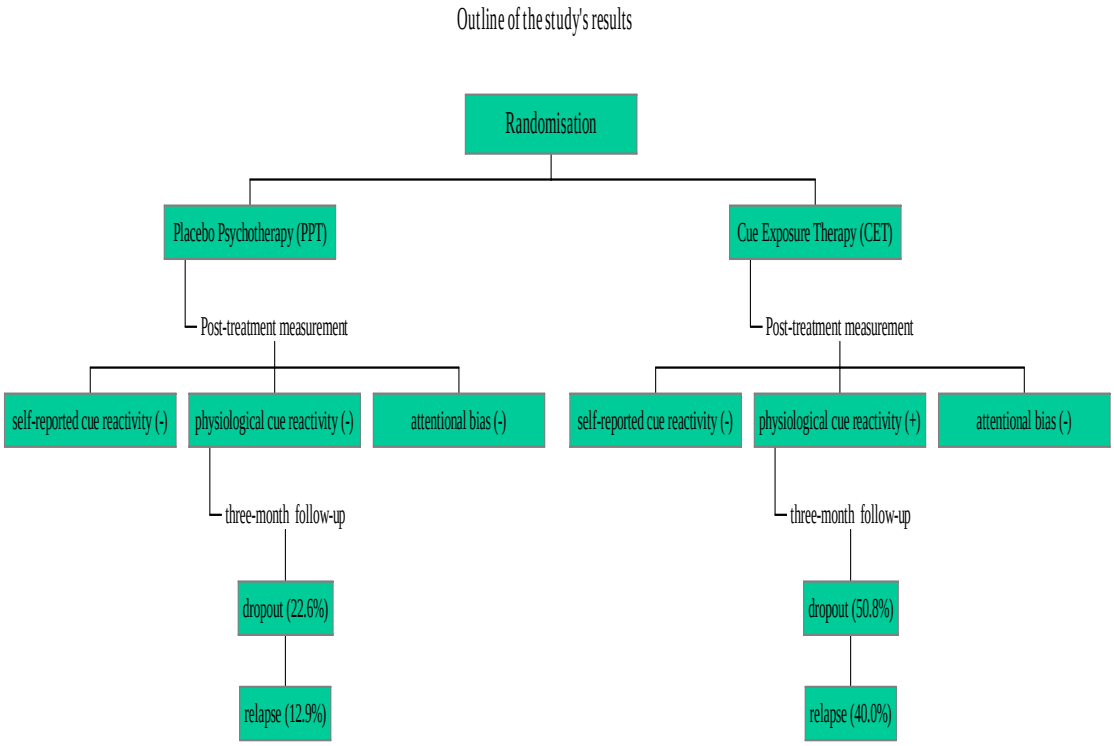


Figure 1

*CET extinguishes drug-related cue reactivity*

We observed a significant effect of CET on skin conductance response to a heroin-related cue compared to placebo-psychotherapy. However, effects on cue reactivity were only of limited coverage (no effect on any of self-reported measures, or stroop data) and the effects on skin conductance only remained for a short period of time (this thesis, chapter 5).

The Incentive-Sensitisation theory of Robinson & Berridge (1993) could provide some explanations why extinction-based therapies are not effective or even damaging. In their theory, Robinson & Berridge state that through repeated drug-intake, long-lasting neuro-adaptations in the brain system occur, which make the addict hypersensitive ("sensitised") to drugs and drugs-associated stimuli. It might be that through CET, neuro-adaptations layered 'on top' of the neuro adaptations responsible for sensitisation are extinguished, but that the actual underlying neuroadaptations are resistant to extinction and therefore persist (Robinson & Berridge, 1993).

From a more clinical point of view; we treated a group of participants who used heroin for approximately nine years. In our intervention, *at least* nine drug-related

individualized cues were used during exposure sessions (i.e., preparing tin foil, vaporizing heroin, listening to heroin-related music). Assuming that in 'real-life' they performed this ritual three times a day during the last nine years; this would at least lead to roughly 10.000 associations in the presence of drug-related cues. Intuitively, one could also state that nine one-hour sessions of cue exposure to these drug-related cues with response prevention can have only limited effects. In addition, why do people relapse into smoking behaviours after years of abstinence, while in all these years they were exposed to smoking cues and thus ‘ naturally’ experienced thousands of CET sessions with response prevention? Was perhaps the theoretical model of CET for addictive disorders quite naïve to begin with? If so, how come we do find positive results of CET for the treatment of anxiety disorders?

While CET has not proven to be effective for addictive disorders, clear results are shown within the field of anxiety disorders and obsessive-compulsive disorders (Araujo, Ito & Marks, 1996; Mineka, Mystkowski, Hladek & Rodriguez, 1999). For example, in a CET study 36 participants, who were highly afraid of spiders, were exposed to a tarantula and their habitual response of avoidance was prevented. Within one cue exposure session of a maximum of two hours this treatment was highly effective in reducing the fear level of all 36 participants (Mineka et al., 1999). Positive effects of CET on treatment outcome for panic disorder patients with agoraphobia can maintain for at least a year (Ito, De Araujo, Tess, De Barros-Neto, Asbahr & Marks, 2001). The basic assumption from which CET is originally generalized from anxiety to addictive disorders, is that in both disorders, through the process of classical conditioning, conditioned stimuli (i.e., a spider or a needle) have become to evoke conditioned responses (CR's) to cues (i.e., fear or craving). The idea is that one can extinguish these CR's by preventing participant's habitual response (i.e., avoiding or drug using).

A first problem within this line of reasoning is that the main difference between these disorders is that for anxiety disorders conditioned responses are 'aversive' (fear) associated with avoidance behaviour whereas for addictive disorders 'appetitive' (craving) associated with approach behaviour. Presuming this would not be a theoretical problem, one could also extinguish for example deviant sexual behaviour or craving for chocolate by exposing people to relevant appetitive stimuli while preventing their habitual response. To our knowledge this has not been examined. However, studies examining the effect of CET for bulimia nervosa, a disorder associated with appetitive features (cravings), have also failed to show clear results (Carter & Bulik, 1994; Bulik, Sullivan, Carter, McIntosh, Joyce, 1998). Bulik et al. (1998) examined the

contribution of CET within cognitive-behavioural therapy and concluded "Exposure with response prevention is an expensive and logistically complicated treatment that does not appear to offer any significant additive benefits that are proportional to the amount of effort required to implement the treatment". The question whether appetitive responses are more resistant to extinction than aversive responses remains a subject of debate (see Conklin & Tiffany, 2002; Marissen et al., chapter 6).

A second problem could be that short-term cognitions accompanying 'aversive' conditioned responses are often irrational. Examples could be: "If I do not wash my hands right now, something terrible will happen to me" or If I do not avoid this spider right now, I will die of fear". Through CET with, for example phobic patients, irrational cognitions will be proven to be wrong; if they are prevented to perform their habitual response, which is often avoiding, patients become aware that they do not actually die of a panic attack when being confronted with their fear-related stimuli. The resulting cognition could be " I did not avoid the spider, let him walk over my hand and I am still alive".

In contrast, short-term cognitions accompanying 'appetitive' conditioned responses often have a rational nature such as "If I smoked heroin right now, it would make me forget my problems" or "Smoking heroin right now would make me feel incredibly good". After CET, cue reactivity to the drug-related stimuli might be reduced, however the content of cognitions remain the same. The resulting cognition after CET could be "I did not use heroin, but if I would use it right now it would still give me pleasure". Positive outcome expectancies in combination with low self-efficacy ratings could lead to relapse after a period of abstinence (Marlatt, 1996). A limitation of our study is that we did not assess drug-related 'outcome expectancies'. We did examine the influence of CET on self-efficacy in drug-related high-risk situations and found no effect compared to placebo-psychotherapy. Perhaps the limited efficacy of CET can be partly explained by its incapability in adjusting cognitions.

At a physiological, non-cognitive level, the decreased physiological cue reactivity (skin conductance responses to a heroin-related video) in the CET group compared to PPT at post-treatment indicates that (partial) extinction did occur as a result of therapy.

This is in line with what Conklin & Tiffany state according to their review on CET studies (2002), "Extinction is a real phenomenon; it simply may not operate in the way we once presumed that it does".

*Less cue reactivity does not prevent early dropout and subsequent relapse into drug use*

The main goal of cue exposure therapy is to extinguish cue reactivity in order to reduce relapse among addicts. Heather, Stallard & Tebbut (1991) showed that heroin abusers reported subjective craving as the most important motivational reason for relapse. There are, however a number of critical assumptions to be made when it comes to the relationship between cue reactivity and relapse. Up until now, effect studies concerning cue exposure therapy have failed to show a significant reduction in relapse rates among addicts (Conklin & Tiffany, 2002; Havermans & Jansen, 2001). A possible explanation for this phenomenon could be that cue reactivity is not that good a predictor of relapse after all (Havermans & Jansen, 2001). In the current study we found self-reported and physiological cue reactivity to be unrelated to relapse into heroin use. Similarly, Drummond et al., (1990) stated in their article about cue reactivity and it's implications for CET: "In summarizing over 20 years of research and a large number of studies, it is necessary to come to the disappointing conclusion that no published human study so far demonstrated that conditioned responses to environmental cues represent a causal factor in relapse in either drug or alcohol dependence". Ten years later he stated that "Since the simple causal relation between craving and relapse is generally not supported by research perhaps the assumption behind cue exposure therapy is relatively naive and uncritical "(Drummond, 2001).

Perhaps another mechanism, not directly linked to cue reactivity is responsible for relapse into drug use. Robinson & Berridge state that the brain systems which become sensitisized by repeated drug use, are not the neural systems that are associated with drug-'liking'. Instead, the neural system that is sensitisized is the one associated with drug-'wanting', where attractive salience is attributed to drug-stimuli, which could lead to actual drug seeking. They further state: "It is interesting to consider that the neural system responsible for incentive salience attribution can sometimes produce goal-directed behaviour (wanting) not only in the absence of subjective pleasure, but in the absence of conscious awareness of "wanting" itself" (Robinson & Berridge, 1993).

So, is cue reactivity the mechanism on which we should aim our interventions to begin with? In line with the incentive-sensitisation view we found pre-treatment attentional bias, and not craving, to be a predictor of relapse at three-month follow-up. Drug-related stimuli (in this case heroin-related words on a computer task) 'grab the attention' associated with drug-'wanting', and can predict goal-directed behaviour.

*Higher dropout and relapse rates are observed after CET*

Some researchers predicted that CET would have limited efficacy for the treatment of addictive disorders (i.e. Robinson & Berridge, 1993; Drummond, 1990) and some (i.e., Marlatt 1990) did even express their concerns about the possibility that CET might extinguish conditioned compensatory responses to drug cues, which could lead to an unintended 'paradoxical increased sensitisation effect'.

The main conclusion of our study is that we simply do not know what happened after providing our population with CET. We can only retrospectively try to search for 'logic' explanations for these contradictory findings

Perhaps we did 'trigger' certain sensitisized neural systems by exposing already vulnerable people to highly 'wanted' drug-related stimuli. It could be that through the sight or smell of the drug-related stimuli, the sensitised brain areas associated with "wanting" (and thus those areas responsible for goal-directed behaviour even in the absence of conscious awareness) become in some way activated. This would have serious consequences for CET as an intervention, especially those treatment designs that use priming doses of the substance to elicit craving.

Also, the fact that our CET-group, after being intensively confronted with heroin-stimuli relapsed into heroin use more often at follow-up made us wonder if perhaps some kind of ‘rebound’- or compensation effect occurred which caused this unexpected findings. Indeed, the focus within therapy lies on availability of the drugs; preparing the drugs but not being able to use it. What we know from food dieters is that they often report that when they deny themselves particular food, they will eventually ‘crave’ it, which could lead to the paradoxical effect of overindulgence after a period of abstinence (Mann & Ward, 2001). Studies examining this rebound effect, measured by a behavioural component are remarkably scarce. However, studies on thought suppression show that when participants are asked to suppress certain thoughts, they often fail at doing this followed by a rebound of unproportionally frequency of the ‘forbidden’ thought (Wegner, Schneider, Carter & White, 1987). This so-called ‘ironic-process model’ is shown in healthy subjects (undergraduate students) even when forbidding them to eat an only moderately appreciated food for five days (Mann & Ward, 2001). Most Cue Exposure Treatments have a strong focus on total abstinence, the highly wanted drug is supposed to be rejected *forever* and it cannot be excluded that this emphasis in combination with the exposure-component could lead to paradoxical effects. However, research on behavioural rebound-like reactions as a response to deprivation of highly appetitive stimuli is lacking.

Another question arises from clinical cue exposure practice when observing reactions of abstinent addicts to drug-related stimuli. We often observed participants reacting with high stress and anxiety levels to individualized drug-related cues. Their natural reaction (even after intensively explaining the treatment rationale; i.e., trying to elicit craving-levels as high as possible) was to adopt a coping-strategy of cognitive avoidance. Examples of this are 'avoiding' the cues by focusing on neutral aspects in the room, or attempts to distract the therapist by repeatedly changing the subject, as long as the attention is drawn away from the cues. Following the CET protocol, the therapist should be aware of these defence mechanisms and discuss them with the client in the light of the treatment rationale, and switch back the attention to the cues to elicit craving. In other words, the therapist 'breaks the resistance' of the client by forcing him or her to give up their habitual coping strategy in order to achieve a higher goal; extinction of cue reactivity. This is what makes CET a highly confronting intervention and often requires maximum persuasive skills of the therapist. Retrospectively, we can wonder if it is a good strategy to force people to give up their habitual coping resources, especially since they might be quite 'healthy' or beneficial. After the extinction phase, participants did react to drug-related cues with less stress and anxiety. So, we might additionally and unintentionally have extinguished fear for drug-cues, a perhaps quite useful defence mechanism in a phase of treatment where people are still rather vulnerable for relapse.

*The future of Cue Exposure Therapy: Must we keep on trying?*

To conclude, following several CET studies finding no evidence for CET as a potentially effective intervention for addicts, we now have evidence from a randomised controlled trial that basic CET can even have negative effects on the treatment outcome among abstinent heroin dependent clients in residential treatment.

Of course, performing this 'basic' CET in the context of a clinical setting leaves us unknowing what effects would have been if we performed it in 'real-life situations'. In addition, many drug-users in residential treatment are poly-drug users (in our sample 97%), which means that CET sessions should most favourable have been doubled or even tripled in an attempt to extinguish reactivity to all cues for multiple types of drugs. However, for ease of interpretation we wanted to focus our basic intervention on one type of substance.

If we had chosen to combine CET with coping skills training, we retrospectively could not have known what caused effects, the cue exposure therapy with response prevention or the coping skills training.

Or, as Conklin & Tiffany (2002) put it "There is much that can and should be done to improve basic cue-exposure therapy without confusing matters by combining it with another treatment approach of uncertain impact". From clinical observations, CET is an intensive, confronting therapy which requires a lot of effort, both from clients and therapist. However, the model of strict cue-avoidance is not advocated either. It would be fairly impossible to avoid all drug-related cues, and even when one would attempt to do this, internal cues such as drug-related memories or moods are very difficult to avoid. Since many abstinent addicts do experience craving, we should design interventions that focus on 'handling ' or learning to cope with this craving in a structured and protocolized manner.

From an ethical and clinical perspective, as long as we do not know exactly what we are doing and what harmful effects it might have on participant's treatment, we should be very careful in using this intervention in a residential setting.

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# Appendix I Cue Exposure Protocol

## Protocol Cue Exposure Therapy

This protocol roughly describes each session of Cue Exposure therapy. The therapist is supposed to follow this protocol for the complete duration of Cue Exposure Treatment. Because the treatment is based on the client's personal experiences with heroin, the cues offered will differ between persons. This is why the offered cues per session will not be described in detail in this manual.

After describing all nine sessions, three possible dilemma's will be discussed; the client reports no craving, reported craving does not subside and the problem of using cocaine next to heroin. This manual provides guidelines for the therapist how to handle each dilemma. Finally in the back of the manual, 3 supplements contain the following:

1. The craving interview: this interview is focuses on identifying highly individualistic cues in order to maximize participants craving levels.
2. Coping strategies which can be applied after the exposure sessions in case of remaining craving.
3. A detailed example of a cue exposure treatment using a fictive client.

### Important aspects in Cue exposure therapy

# a good therapeutic alliance
# well-defined structured sessions
# emphasizing the treatment rationale during all sessions
# emphasizing the (natural) extinction-process
# be creative in eliciting craving levels
# Let the client take initiative
# be alert for cognitive avoidance
# make sure that at the end of each session there is room for an adequate 'talk-down', using coping-strategies to diminish remaining craving

CET session 1.

Duration 60 minutes.

Schema: 1. Introduction
2. Treatment rationale
3. Craving interview
4. Evaluation

*1. introduction*

A number of issues are important to cover in this first session.

Introducing yourself

Repeat rationale

Duration of treatment: nine sessions and three assessments

Content of first session

Emphasize that asking questions is always possible

Emphasize that it is of great importance for this treatment to succeed that the client understands the rationale of the treatment.

*2. treatment rationale*

It is advised to learn the treatment rational by heart; it is one of the most important aspects of the treatment and needs to be explained to the client in a clear and structured manner. Below we will describe the rationale as it could be explained to the client. In case of any uncertainty whether the client understood the rationale it would be wise to let him or her to repeat the rationale in his/her own words. It is also important to emphasize that this is not a test but simply a way to check if the therapist was clear enough in explaining the rationale.

Cue exposure is based on a theory that presumes that craving for a substance (for example heroin) is a form of learned behaviour. Maybe you have heard of the Pavlov experiment? Pavlov did an experiment with a dog. We know that when a dog sees his food being put in his plate he starts salivating. What Pavlov did was ring a little bell just before he put the food in the dog's plate. When, after doing this several times, he stopped giving the food, but just rang

the bell, the dog still began salivating. The dog had learned to link the sound of the bell with his getting fed. When however Pavlov rang the bell a couple of times without providing the food, the salivating diminished and finally stopped. The link between the bell and the food was, as we call it, extinguished.

This experiment provoked a lot of research into this 'learned behaviour', and this way we came up with a good explanation for the craving for heroin that addicts often experience. When you are addicted to alcohol, drugs or medication you often have the feeling you cannot exist without these substances. The need or desire for the substance is sometimes so strong that is seems impossible to resist. There often are many different psychological reasons to experience such craving like being depressed, unhappy or tensed. Sometimes however, it seems there is no exact reason for experiencing craving. There must have been moment when it seems as if you react automatically to craving. There is a good explanation for this.

The moment an opiate-user sees or smells heroin, his body makes itself ready to receive and process the heroin. Seeing and smelling heroin almost always proceeds the using of heroin, so the body seems to know that it is going to get heroin when it sees or smells the heroin (think of the Pavlov- experiment!) The sight of heroin predicts the taking of heroin because this almost always had been the case. You know that taking heroin has physical consequences: for example, your heartbeat will slow down and your body-temperature and blood pressure change. Let us for know stick to the heartbeat.

The body of an opiate user smelling heroin can almost always assume that it's going to get heroin. Heroin however disturbs the balance of the body, and our bodies don't like that. Because of that, something strange happens: as soon as the body knows heroin is going to enter the body, it takes action to prevent the disrupting effects of heroin. Like I told you, one of the effects is a slowing down of your heartbeat. What do you think happens to your heartbeat even before you take heroin, the moment the body expects that heroin is going to be taken? At the smelling of heroin, the heartbeat will go up. The body reacts with an opposite action to reduce the effect that the heroin will have when it enters the body. A process you might well know is that every time you take heroin, you will experience less pleasure that the previous time. This phenomenon is known as tolerance. The opposite physical response to preserve the equilibrium in your body is called the anticipating opposite response. So when

an opiate user is walking into a dealing house, his body will react with the opposite effect that heroin will have, entering the body (the heart will beat faster). Do you understand until know?

What is even more fascinating is that the opiate user experiences this faster heartbeat as a strong, almost irresistible need to use heroin. The physiological symptoms are being interpreted as craving. An opiate user who always uses his heroin in a particular chair, will, when seeing the chair, react with craving for heroin. Every person has his own particular situations that are linked to the use of heroin. Not only heroin will be a good predictor the using of heroin, but also attributes that belong to the using of heroin (like a syringe, foil), the place where you normally use heroin, the mood you're in when using, thoughts that go through your head, maybe even particular music. When all these things get linked many times to the use of heroin they will get to be predictors (cues) that will evoke physical responses and subjective craving symptoms.

So when someone who regularly uses drugs encounters one of his personal cues, the body will prepare itself and the person will feel the need to use.

A solution for quitting heroin could be to avoid situations in which the person might encounter these predictors (cues). It will however be impossible to avoid these situations forever. It is a good possibility that you one day will be in such a situation and encounter a predicting cue. So it is very important that these cues will loose their predictive value. So now we will go back to the beginning of my story where I told you about Pavlov's dog.

When the bell was rung a few times without presenting the food, the dog's salivation diminished and finally even stopped. The ringing of the bell (the cue) lost its predictive value. So, by exposure to the cue (the bell) the preparing physical response disappeared.

In the treatment of addicts, this same process is made possible by exposing the addicted person to his essential cues that in the past predicted the taking of drugs. During cue-exposure therapy these cues will not be followed by the use of drugs. By doing this the cue will loose its predictive value, the anticipating opposite physical reaction will extinguish, which will reduce the chances for relapse into drug use. I realize this has been a very long story. Do you have any remaining questions?

Discuss the theory and process of cue-exposure again and try to let the client do the talking. This is done to check if the client really understands the way cue-exposure works. Additionally, the following points can be discussed;

•Overdose: An important facet of the anticipatory opposite response (the compensating effect) is that in an unfamiliar situation the compensating response might come to late or will not occur at all. A possible result of this can be that a previously tolerated dose of heroin can now lead to an unwanted overdose because the body is not prepared for what's coming.

•Addicted Vietnam-veterans: When essential cues are not available, the anticipating response will fail to occur and there will not be any craving for drugs. A well-known example of this is seen with returning addicted Vietnam veterans that kicked their habit and stayed abstinent without many problems. This percentage of abstinent veterans (65%) sharply contrasts with the percentage of 'normal' detoxified addicts (10%) that remain abstinent, and can solely be attributed to the fact that for the veterans the situation in which they used drugs is completely changed. They do not encounter their most essential cues anymore.

Ones again emphasize the importance of understanding the theory and goal of cue-exposure therapy and that it will be discussed many times more in the first session.

Tell the client that at the end of every cue-exposure session he will learn coping strategies to prevent the existence of any remaining craving when returning to his treatment-centre.

*3. Craving interview*

Explain to the client why you do this interview and motivate him/her to think hard about which cues are important to him/her. When a client can't come up with any cues it is possible that he doesn't want to be confronted with his period of being addicted or maybe is afraid to resurrect old memories. If this is the case, try to discuss this and explain the rationale behind the cue-exposure once more.

The first step of the treatment has been made. The next step is to make a list of cues that are important to you. One important cue we already know of is heroin. Are there any other cues you can think of, maybe in the manner how you used your heroin: do you smoke or inject your heroin? Maybe you have some fixed rituals when using, or maybe you always use in the same environment? Even some feelings can be very important, like feeling lonely?

Let's do this: I have a list of questions to systematically make an inventory of important cues. Cues that are important to you we will use as much as possible in the cue-exposure treatment. Some cues will be present literally, like for example heroin, a syringe/ pipe, or maybe particular music. Other cues will be exposed in another way, for example by trying to bring yourself in a certain mood by imagining you're in a certain situation. We will try to extinguish the most important cues in eight sessions.

*4. Evaluation*

- Point out that at the end of every session there is time to evaluate the session and go over any questions the client might have.
- Provide a thorough 'talk-down' when the client is still tensed and experiences craving at the end of the session.
- Ask the client if he or she has any questions.

This treatment will probably be a little tricky, especially in the beginning, because you'll be confronted with just the things you wanted to get rid of. It is a complex treatment that requires lots of effort and perseverance from you. In the beginning you will experience a lot of craving and tension when facing the cues, but you will notice these feelings diminishing after a while. It is very important not to return to your treatment centre with a lot remaining tension or craving. This is why, at the end of each session we will take time to talk about how you felt the session was going and to practice coping strategies to handle any craving you might have when you're back in the centre. I know this was a whole lot of information I gave you. In the next session I will begin by summarizing the most important things that were said today and if you have any questions after that I can answer them for you. After that we will start the actual cue-exposure therapy. Do you have any questions at this moment?

## CET session 2

Duration 60 minutes.

Schema:

1. Schema and rationale

2. cue exposure
3. evaluation session and coping strategies

*1. Schema and rationale*

- make clear what is going to happen this session
- Check again if the client understands the rationale behind cue-exposure; if not, try to explain once more.
- Ask client if maybe he remembered important cues which were not mentioned in the first session.

*2. Cue-exposure*

- Start with explaining the rules concerning cue-exposure:

I want to start with explaining the rules that apply to cue-exposure. The most important rule is that you do not try to resist when I try to elicit your craving. By this I mean that you cannot show any avoiding behaviour. It is very important that you concentrate on the cues completely and that you focus your attention on them. This is the only way in which extinction of the cue can take place. A way to do this is to think out loud about what happens and what thoughts come to your mind when focussing on the cue. I will help you do this in the beginning, by asking questions and by leading you through the process of touching, smelling etc. Avoidance behaviour can be, for example, focussing your attention on something completely different, look the other way when presented the cue, going to the toilet in the middle of exposure or maybe asking questions about the treatment. Of course it is ok to ask questions but you'll have to save them for the end of the session.
You don't have to panic when you notice having extreme craving. The purpose of the cue-exposure is to experience these extreme feelings of craving and although you may not believe it, these feelings will diminish after a while even when you keep eliciting them. This is the start of extinguishing the intensity of the cue.
To see if the feelings of craving are diminishing en finally extinguish I will ask you regularly during exposure how much craving you feel at this exact moment. I want you to try to describe the cravings on a scale from 1 to 10, in

which 0 means ‘no craving at all’ and 10 means ‘extreme feelings of craving’. Doing this I can see that the cue really is extinguishing and at what rate it is diminishing. I you however, do not experience any craving we must find out what important part of the cue is missing. In every session we will build up the cues. In this session we will start with tinfoil. I propose that I will put in on the table and you will describe to me what this does to you, how it makes you feel and how you used to use the tinfoil. The purpose is to let the craving become as strong as possible. Don’t be afraid of the feelings of craving, because before you leave this room I will make sure the craving has subsided, maybe by using one of the coping strategies.

It is important that the therapist makes sure the client doesn’t show avoidance behaviour, which means that the clients has to be encouraged to touch the cues, to smell them and to tell the therapist what happens. The therapist can also function as a model for the client. It can be very frightening to the client to touch and smell and talk about heroin and the rituals of using it. The client might be scared to loose control, can get very ashamed and might want to leave the room. The exposure can be extremely frightening and because of this it is very important that the therapist is a good model to him or her. Go over it with him/her, join him/her, don’t be embarrassed yourself to do this. Encourage him and keep stimulating him, even when all goes well. “You can pick up the syringe… how does it make you feel… can you taste the feeling… look at it very thoroughly…. How about your feelings of craving…? Can it become even worse? And how…

After a few sessions it is possible for the therapist to take his distance and to withdraw a little. This however is only an option if the client can imagine himself very well in the situation. In this case it is very good to withdraw, because we don’t want the therapist to function as a safety-signal.

At the beginning of cue-exposure, the verbal VAS-scale is very important in checking if a cue really elicits craving. If the craving is not elicited, discuss with the client why this is not happening. Maybe he or she is afraid to 'surrender 'completely to the situation, or maybe the ritual is not realistic enough? Try to make it a little more difficult/ real by using music or imagination. If this doesn’t work you might try to burn a little heroin to elicit the craving. Be aware that a drug-related memory that has come up in eliciting craving can become a new cue that can evoke craving feelings.

*3. Evaluation*

- Ask the client how he experienced the cue-exposure
- Provide a thorough talk-down and discuss a coping strategy.

## CET session 3-8

We will not describe these sessions apart from each other because all sessions from now on will follow the same structure. The only difference will be the content of the cues. It will be apparent that these will differ with each client and that the rate of extinction will be different for each client also.

Duration: 60 minutes

Schema: 1. preliminary talk
2. cue-exposure
3. recap and coping strategies

*1. Preliminary talk:*

Points of interest every session will be the rationale, the client's experiences following the previous session, and a preliminary discussion of the following session. The preliminary discussion focuses on the content of the cues that will be used this session. Take care each session will be structured so that the client knows what is going to happen beforehand.

*2. Cue-exposure*

The sequence and the way in which the cues are offered to the client are depending on the levels of cue-reactivity and the rate of extinction of the cues with each client. If a client displays a lot of craving, and little extinction of the cue during the second session, it is useful to repeat exposure of this cue, without adding anything to it in the third session. There is no rule that says every session needs to handle a new cue. It is however also possible that the client displays very little craving, being exposed to the first cue. We than have to find a cue in this session that will elicit craving.

In this case, when a clients displays very little or now craving at all, the therapist has to try to keep motivating the client to follow through with this treatment, without getting bored or annoyed. It is the therapists' job to keep the client to be confronted with heroin related information. Keep referring to the 'why' of this therapy, even when it's not going as planned. If, after two sessions, there is still no success in finding craving-eliciting cues and the client does not seem very interested in following through with the therapy we advice to stop the treatment.

After session 7 it is very important to keep more distance. The client knows what is expected from him and by now knows how the cue-exposure works. The therapist needs to make sure he or she is not getting to be a conditioned safety-cue. By doing this we prevent that the clients will only display diminished craving when the therapist is present.

*3. Recap*

Every session it remains important for the client to be able to tell what he experienced during the cue-exposure and how he feels the treatment is evolving. A thorough talk-down is important in keeping the client motivated.

## CET session 9

Duration: 60 minutes

Schema:
1. preliminary talk
2. cue-exposure
3. recap
4. evaluation of the treatment.

Take good care that the treatment is concluded in a positive way. It is better not to present any new cues in this final session.

*4. Evaluation of the treatment:*

In this evaluation the client's perception of the treatment is discussed in detail. The following aspects will be discussed.

- Did the client feel the therapy was useful to him/her?
- Has the rationale been meticulously explained?
- Were the sessions constructed in a good way?
- What did he/she think of the quantity of sessions?
- Were the cues realistically enough?
- Was there enough room to ask questions?
- Did he/she believe the therapist was experienced?
- What can be adjusted, should anything be changed about the treatment?

## Dilemma 1. The craving can not be elicited

In the case of not being able to elicit craving (the VAS-scale score remains below 3), it is very important to go over the rationale once more. Explain to the client that when they do not experience craving, no extinction can take place. Tell the client that all efforts should be aimed at eliciting as large a craving as possible during exposure. As soon as the client is convinced that craving is a necessary step to get rid of the addiction, attention is focused on identifying reasons for failure of eliciting craving. Several causes may apply:

- The client is too passive during the exposure. Clients may avoid touching or smelling, or approaching the cues. Discuss what makes it so hard to have these things done. In most cases someone is afraid to surrender to the craving (what if it does not go away again?). Clients could also be ashamed. In both cases, the therapist can act as a role model. Ask the client to mimic you, so they will take it further step by step. Reinforce them if all goes well and motivate them to go a bit further. If the client is afraid the craving will get too high and (s) he will actually use drugs, agree on how the client can get control again, or discuss how the therapist will react (firmly put the client right, intervene) if this should happen.
- Cognitive avoidance: the client thinks of other things than the exposure and distracts himself in order not to feel the craving. By asking, as a therapist, to firmly realise what the client is doing and how this makes them feel, the client is forced to acknowledge the feeling of craving. Ask them what they see lying on the table, what it looks, feels, and smells like. Ask what it would be like to use this. Ask what it feels like if someone is about to use. By having the client verbalize what's going on in their minds and by stimulating them to actively handle the cues, the cognitive avoidance is disturbed.
- Important cues are missing. Investigate together which cues are not right, or which cues are missing in the session. Be sure to actively engage the client. If necessary, assess once more in which situations someone normally used. In addition, make sure if there are unintended cues present, that inadvertently prevent craving. Obtain the missing cues and continue the exposure.
- The setting is too artificial. It can occur that despite the presence of the most important cues, the situation is still too artificial. Imitating the ritual from the start could help, e.g., the client imagining what they were doing five minutes before. The therapist

can stay at the background during this period and should come into the picture when the cues that are present are actually going to be touched. Try to imitate the real situation as much as possible.

- The presence of safety signals. Safety signals such as the presence of the therapist can hinder the rising of craving. In this case one has to choose between two evils: your presence, especially in the first phase of the therapy, is necessary to ensure the execution of a good exposure, but also causes the craving not to increase enough. In this case, teach a good exposure, and as soon as the client is capable of executing a good exposure themselves, the therapist's presence or absence can be experimented with, e.g., sitting with the back toward the therapist, or the therapist sitting in the corner of the room. Do not ever leave the therapy room, but stay in the client's presence.

- During the actual exposure, the client is more concerned with the evoked emotions (for example anger, because heroin was the reason for his admittance to the clinic) than with the actual elicited craving. Although it is understandable, clients are concerned with their emotions, in the process of cue exposure it is not wise to focus on them. During exposure the purpose is to elicit craving and to let it extinguish again. By focussing on the evoked emotions and not explicitly on the feelings of craving, it could happen that the craving will not rise and cue exposure is of no use. Ask the client explicitly about the feelings of craving. This point should not be confused with the evoking of a certain emotion for eliciting craving. In the latter case the evoking of emotions is used to let craving-levels rise and is as such used as a cue.

- If after session 3 the therapist has not succeeded in evoking any craving and the client is not motivated to go on with cue exposure therapy, it is advisable to stop the therapy. It is impracticable to have 6 sessions with an unmotivated client who is bored and experiences no benefit of this treatment. If after two full sessions of cue exposure the client shows no signs of craving you may conclude that the most important cues have been used and alternatives have been sought for.

## Dilemma 2: Craving does not seem to extinguish.

In the case of craving not diminishing, different explanations can be offered:

- During the session the client is confronted with several cues in a row. Suppose craving gets very high when the client is exposed to heroin. After this the client is expected to perform his 'users ritual' and he has to focus on the scent of the burning heroin. Doing this a lot of cues have been offered in a row which elicit craving in different ways. It is very understandable that the feelings of craving are not diminishing. If a client reacts to the sight of heroin with a lot of craving, wait until the craving extinguishes by itself before offering a new cue.
- Another possibility is that when the client experiences a lot of craving he is not focussing on the feelings of craving itself but is impressed by the feelings this evokes. In this case the focus is not any more on the cue and the craving. Motivate the client to start focussing his or her attention on the cue and the elicited craving again.
- When it takes a long time for the craving to diminish it is important to tell the client it is very good that he is able to let the craving get this high, and that he has to hold on without actually using heroin. It is possible that that for this client the available time for a cue exposure session is not enough. In this case prolong the session until the craving has at least diminished a little bit. If this takes an extremely long time the therapist does not have to wait until all craving has extinguished, just diminished in such that the client sees the result and experiences rationale of the therapy. In the next session the therapist will have to offer this same cue to proof the craving will finally extinguish by itself.

## Dilemma 3. Cocaine use

A fair number of clients will, next to heroin be dependent on cocaine. In this study however, the focus is on heroin use. This is not to say that no attention whatsoever will be given to the use of cocaine. Cocaine will be handled within the cue exposure therapy, when necessary, as an important cue for the use of heroin. This can be seen in the same way as alcohol dependency. If a person is accustomed to drinking 4 glasses of alcohol before the use of heroin, the use of alcohol is a strong predictor of heroin use. Offering of a cue like this (alcohol, cocaine) can only be done imaginary or with the use of paraphernalia (a glass of beer, white powder). Using it is absolutely out of the question!

When the use of cocaine has nothing to do with the use of heroin, in other words; if the two addictions can be seen separately; the cocaine dependency will be ignored in this therapy. An example of this is the use of cocaine primarily at parties and the use of heroin the remaining time.

An example: John regularly uses heroin and cocaine in which heroin primarily functions as a downer for the effects of cocaine. In the first sessions the therapist will be primarily offering heroin cues. In a later session you will ask John to describe in detail a situation in which he first uses cocaine and then heroin. It is important that the situation becomes as concretely as possible. The therapist has to bring about the effect that John has the feeling that he actually is under the influence of cocaine. Ask as many questions about the situation as you feel necessary and reflect in John's words on his perceptions of the situation. When John has been brought to a situation in which he feels like he is under the influence of cocaine, ask John how much craving for heroin he experiences. When the craving is higher than '2' on the VAS-scale, the exposure to heroin can start. If the craving does not exceed '2' the therapeutic situation is not complete and the therapist must look for more cues that will evoke the right response.

# Appendix 1. Craving Interview

Q. 1.

When was the last time you experienced craving for heroin and in what situation were you when this happened? This doesn't have to mean that you really wanted to use heroin at that moment: it is very possible you were trying to get over these feelings of craving.

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Q.2.

What thoughts did you have when experiencing this craving?

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And what feelings did you have?

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What physical sensations did you have?

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Q.3

When you experience these feelings of craving, do you at the same time experience withdrawal symptoms?

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Do you at the same time feel symptoms like you have when under the influence of heroin? (like feeling high a.o.)

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Q.4.

Describe the usual situation in which you used heroin in as much detail as possible. (surroundings, the presence of others, emotions, rituals, food, drinks, tv, music, time of the day)

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Q.5.

What external cues you think are important to you? For example specific situations or times of the day that make you crave for heroin? (specific neighbourhoods, toilets, tram, trains, home situation, film, video, photo, smell, music, people)

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What internal cues normally illicit craving for heroin in you? (feelings like loneliness, joy, sadness, specific thoughts, and specific bodily sensations)

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Q. 6

Could you describe for me in detail a situation in which it is for sure you will get craving for heroin? (time, place, other people, thoughts, feelings in your body, specific behaviour)

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Q.7

What other substances have you used frequently?

Methadone / cocaine / speed / medication / LSD or other trip inducing substances / cannabis / alcohol in large quantities / other…….

In what way did you use these substances together with heroin? (always subsequently, or in combination and in what situations?)

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Q.8

Can you remember if the last few times you ‘relapsed’ after a clean/ abstinent period this was caused or attributed to specific factors or situations?

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## Appendix 2 Verbal 10 point Likert scale

During cue exposure therapy a 10-point likert scale will be frequently used. This is done to describe the amount of craving the client has. The following rules are set for the assessment of the VAS-scale.

- *Give a clear explanation of the scale to the client*

The craving for heroin has to be described as the appeal of the thought of using heroin. How much do you want to use drugs now? It is possible that you feel a strong craving for drugs although you do not want to use it or know you will not use it. For example: you can have a lot of craving for chocolate although you know you will not eat it because you are on a diet.

- *Choice of cues*

Five minutes after offering a specific cue, the decision is made whether this cue elicits enough craving. This is done by using the VAS-scale. If the craving score does not exceed 2 on the VAS-scale, another cue has to be offered or this cue has to be more thoroughly explored.

- *The course of craving*

During the actual exposure to the reactive cue the therapist will ask the client every 5 minutes to describe the amount of craving he experiences with a number between 0 and 10.

## Appendix 3. Coping-strategies at the end of each session

• Relaxation

By the use of relaxation exercises it is possible to reduce craving. Clients become aware of tension in their body and learn to relax their muscles and to change their tensed feeling in a more calm and relaxed feeling.

• Alternative behaviour

Usually, when people experience craving it is limited to 'risk-moments'. Often, craving will be reduced in a 'natural' manner; in general, people do not crave drugs for hours and hours in a row. However, when focussing on feelings of craving intensively it can take longer for the craving to diminish. When performing alternative behaviour, there is less 'space' or attention capacity for feelings of craving and therefore the craving will most likely be reduced. This is a relatively simple coping strategy, which can be applied in various forms, and often clients already use this strategy themselves as a way of handling craving. One way is to 'distract' clients by asking them to tell stories about non-drug related subjects such as things they like to do for a hobby, work or friends. Or, it is possible to make a list of activities with the clients, which can be performed whenever it is necessary to reduce craving. Usually these are activities that are impossible to perform simultaneously with heroin use such as doing sports, doing the dishes or taking a shower. Another possibility is to let clients directly perform an alternative task such as drawing a picture.

• Negative/ positive consequences

An effective manner to reduce craving is to think of negative consequences of drug use. Ask the client about why he or she decided to quit heroin and explore as many reasons as possible. Make sure to find reasons that are specific for this client, sometimes it is helpful to write this reasons down on a paper. Sometimes, a negative mood state can be triggered by focussing only on the negative side of drug-use. Therefore, this coping strategy can be best applied by also discussing the positive side of being abstinent. Again, find as many reasons why life is better without drugs, positively reinforce the client and write down the positive consequences.

• Negative/ positive imagination

After discussing and writing down negative consequences of drug use and positive consequences of abstinence, it is now the purpose to imagine and 'feel' this. Ask clients about their worst period ever when they were still using heroin. Let them describe this period as vividly as possible with details and try to elicit the accompanying feeling. For example "Try to imagine this period where you were sleeping on the street, no money, no friends and try to remember how you felt." After doing this for a few minutes, switch over to a more positive imagination. A possible question could be "How do you picture yourself in a few years from now if you could choose your life?" Again, let the client describe details about how he or she would like to become and feel. Practice this for a few minutes and end the session with this positive imagination.

- Overpowerment image

When being confronted with craving, many clients are overwhelmed by a feeling of 'helplessness', like they are unable to control this feeling. A way to diminish this feeling is to let the client imagine a lively picture of how they can overpower or 'beat' their craving. For example, a client pictured his craving as a huge wave; at first he was flooded by this wave but after some imaginary practice, he could overcome the craving by imaginary 'riding the wave' on a surfboard. Not al clients are susceptible for this coping strategy. Sometimes it can be useful to combine multiple coping strategies to achieve the most effect.

# Appendix 4 Example

Next, a cue exposure intervention for an imaginary client will be described. First, possible answers to the craving interview are given and subsequently a possible treatment strategy. Some cues will roughly be the same for all heroine dependent clients such as the sight and smell of heroin.

However, this example is not intended to 'copy' and apply to every client. The strength of CET is to individualize the drug cues as much as possible. And, there are considerable individual differences in how much time the 'extinction-phase' will last.

*Short description of the client:*

Michael, 29 years, heroin-dependent for 6 years, 2 times residential treatment before, both times ended his treatment pre-mature.

## Craving Interview

Q. 1.

When was the last time you experienced craving for heroin and in what situation were you when this happened? This doesn't have to mean that you really wanted to use heroin at that moment: it is very possible you were trying to get over these feelings of craving.

The last time was when I was at detox, a new person came in, whom I knew from the scene and told me that he just handed over his heroin and tin foil to the staff. ----------

Q.2.

What thoughts did you have when experiencing this craving?

I wish I had that stuff, it would make me feel good and forget my problems for now. But then I thought, "That would be a shame, I have already come such a long way"----------

And what feelings did you have?
First I was really exited knowing that heroin was that nearby, but afterwards I felt sad and angry that I still craved it, I thought I was over that. ----------
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-

What physical sensations did you have?
Sweaty hands, and sick in my stomach, the rest I can't remember, I haven't really thought about it----------
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Q.3
When you experience these feelings of craving, do you at the same time experience withdrawal symptoms?
Yeah, the sweaty hands and the feeling in my stomach are just like when you're sick for heroin----------
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Do you at the same time feel symptoms like you have when under the influence of heroin? (like feeling high a.o.)
Sometimes, when I think about using, and I really want to, it feels as if I actually smoked. But this doesn't happen often. ----------
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Q.4.
Describe the usual situation in which you used heroin in as much detail as possible. (surroundings, the presence of others, emotions, rituals, food, drinks, tv, music, time of the day)
It's around seven at night, I'm sitting at home, watching tv, like I do all day long and Nicky comes around. The last few weeks we tried to cut down but it didn't really work out that way. Normally she would have some heroin on her. She had been making money all day working as a prostitute so she could buy the stuff. When she showed me what she got the craving started. Even the sound of the tinfoil would make me crazy for heroin… Or if we really tried to stop, even the talking about how good it used feel to smoke would make me yearn

for some. During the actual smoking we would sit together with our backs to the couch… ----------

Q.5.

What external cues you think are important to you? For example specific situations or times of the day that make you crave for heroin? (specific neighbourhoods, toilets, tram, trains, home situation, film, video, photo, smell, music, people.)

I used to buy the heroin downtown. I would go there by subway, usually together with Nicky and a friend of ours, named John. What used to trigger the craving too was watching the Trainspotting video. Or listening to the music from Trainspotting…. I used to smoke a joint after using heroin, so when I see or smell a joint I get craving too.

Or when I see other people using…Or when I sit with my back against the couch in the living room where we used to smoke..

When I was hanging out with my friend who encouraged me too not be so dull and join them smoking….

I smoked a few times time in the restroom of this bar, which was close to a friend's house, and when I pass this bar I feel like using immediately…. ----------

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What internal cues normally illicit craving for heroin in you? (feelings like loneliness, joy, sadness, specific thoughts, and specific bodily sensations)

When I feel insecure or nervous…

Or when I've had a really bad day and I want to forget my troubles…Or when I'm really stressed out…

Or after a fight with Nicky… we used to fight a lot about her working as a prostitute…----------

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Q. 6

Could you describe for me in detail a situation in which it is for sure you will get craving for heroin? (time, place, other people, thoughts, feelings in your body, specific behaviour)

I remember a few months ago…. I had just been fired from my job because I came in too late a bit too often… My parents were very angry with me for that and I got into a terrible fight with them After I went home I also got into this big fight with Nicky about her job and me being fired and because I was so fucked up and angry I hit her very hard. After she got up from the ground she ran out of the house…. I didn't have any dope on me so I called this friend of mine and asked if he could come over and bring some….it took him very long…. Well, all in all it took him about fifteen minutes but my craving got stronger by the second… My hands and back got very sweaty and the more I thought about smoking the worse it got….. When my friend finally came around I felt like an awful addict, a real junky. It felt like I would have died if he had taken any longer…. When he got the dope out of his pocket I could finally breath again….----------

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Q.7

What other substances have you used frequently?

Methadone / cocaine / speed / medication / LSD or other trip inducing substances / cannabis / alcohol in large quantities / other…….

In what way did you use these substances together with heroin? (always subsequently, or independent of each other, and in what situations?)

Cocaine was really a party-drug for me… I only used that when going to big raves or when I was really tired and had to go to work…. I almost never used it together with heroin. When I didn't have any heroin but someone did have cocaine I would use some of that…. But normally I just didn't have the money to buy cocaine… Normally I would spend it all on heroin…

I used to smoke weed a lot… normally late at night when I was still feeling the heroin. When I now smell weed I get a lot of craving----------

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Q.8

Can you remember if the last few times you 'relapsed' after a clean/ abstinent period this was caused or attributed to specific factors or situations?

I once ran from the rehab centre…. I didn't feel accepted and it seemed as if I was the only one who was having trouble quitting… I felt like it this wasn't going to help me in any way, I would be addicted for the rest of my life, so I walked out and immediately started using again.

Another time was when I had been clean for a few months. I had made a lot of new friends who didn't use drugs at all… One time they all had gone on holiday or were having a really busy schedule so I didn't get to see them for two weeks in a row. I felt utterly lonely and thought it would do no harm to visit an old friend which I knew from when I still used heroin. I thought he had quit too. Well, he didn't. The moment I entered the room I could smell the heroin in the room and he asked me to join him smoking. He said to me: "One time will do no harm. you can easily quit after that". Well, I couldn't. After the first smoke I never stopped….. I was hooked again.----------

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- With this interview as a guideline the therapist can make a list of the most important cues for this client. During the interview it was obvious that Michael experienced a lot of craving by talking about heroin or using, alone. The therapist can expect that during exposure craving levels of Michael will get very high even without the actual vaporising of heroin. Below we will describe what cues, and in what order could be offered to Michael.

*Session 1:*

craving interview and rationale

*Session 2:*

Michael will describe again what exactly his ritual of using heroin used to be and what paraphernalia he used. After this the tinfoil will be exposed and put in front of him on the table. He is asked to perform his users-ritual. He will tear of the tinfoil according to the size he normally wanted it to be. He starts to smooth it down and tear of the corners. He will also construct the tube for inhaling the heroin in the way exactly the same way he used to make it. The therapist will encourage him to go on and to keep talking about

what he is doing. The craving becomes high and remains at a high level, Michael rates it around '8' at the end of the session. He feels sick and annoyed and claims he does not see how this is supposed to work. The therapist again explains the treatment rationale as clear as possible. To reduce this remaining craving, negative consequences of drug use are discussed in the absence of the paraphernalia. When the craving is below '2' the session is evaluated.

*Session 3:*

The same ritual is repeated. Michael's craving soon becomes as high as it was the last time and the therapist instructs him to remain focussed on the paraphernalia. After ten minutes the craving diminishes, it is now rated a '6'. After another 5 minutes of mimicking the drug-use ritual with the tin foil and the tube, the craving becomes '2'. Michael seems relieved and the therapist explains that what happened is that the craving extinguishes by repeatedly performing the ritual without using the drugs. Michael now seems a bit more confident and agrees on taking on another 'cue'. Now a lighter is being held under the tin foil while he holds the tube in his mouth. Craving levels become immediately high '9'. The ritual with lighter and tube is repeated a few times, at the end of the session the craving is rated as '7'. The paraphernalia will be removed from the table and positive consequences of abstinence are being discussed until craving levels are below '2'. It is emphasised by the therapist that Michael has now dealt with more cues than the last session, that the 'old' cues no longer evoke craving more than '2' and that Michael can effectively and quickly reduce his remaining craving in a simple manner.

*Session 4.*

A video is shown of Michael's old neighbourhood in which he has used heroin often. Simultaneously, the music from Trainspotting is played. He recognises the places and some people in the video that bring out a lot of memories that make the craving become a '9'. Also, Michael feels aggressive by seeing some of his old 'friends'. After the video, the memories and feelings are being discussed, craving levels remain high. Now, the cues of last session are put on the table again and Michael is asked to perform the ritual with tube and lighter a few times. Doing this for about ten minutes the craving diminishes fast and becomes '1'.

*Session 5.*

The progress of the therapy so far is discussed with Michael. He says he notices that his craving reduces during sessions, he does however has some trouble sleeping at night and has a lot drug-related dreams. It is discussed how he could possibly reduce craving in between sessions for example by finding some distraction telling other group members about what he is going through.

Now, a video is shown of a drug user, smoking his heroin. To elicit craving levels as high as possible, the video is shown for 30 minutes; Michael rates his craving level around '8'. He reports feeling 'stoned' as if he has been smoking himself and the therapist explains this is a normal reaction.

At the end of the session a relaxation exercise is done which brings craving levels at '1'.

*Session 6.*

An important risk-situation for Michael is when he is fighting with his girlfriend. The therapist asks him to describe their last huge fight as detailed as possible. By means of a role-play, Michael is asked to imagine as if he is having this fight again and by doing this he feels angry. Craving levels are rated '8'. After the role-play, craving levels fall quickly. Now the neighbourhood-video is played again, craving becomes a '2'. The session is evaluated.

*Session 7.*

The ritual of heroin-use is performed, only now with actual heroin. The smell and sight of heroin when vaporising it on tin foil elicits the craving up to '9'. This ritual is performed a number of times, craving remains the same. The paraphernalia are put away and now the 30-minute video of the drug-user is shown again. In the beginning of the video, Michael rates his craving as '6', after a few minutes, it becomes '4', at the end of the video it is '2'. Michael is asked to visualize his drug-free life in five years and imagine all it's positive aspects.

*Session 8.*

The ritual with the vaporizing of heroin is repeated a number of times. Craving levels fall from '9' to '5'. Now, the situation with Michael's girlfriend is played over again, craving does not occur. Another fight with Nicky is discussed, and also, this does not seem to elicit craving for heroin. Michael says he has been thinking a lot about how to handle irritations and tension with his girlfriend differently to prevent the situation from escalating. Some other alternatives are discussed and the session is evaluated.

*Session 9.*

The ritual with heroin is repeated and after 10 minutes remaining craving is extinguished. All sessions are being evaluated and the therapist summarises all the cues that have been used.

All coping strategies are repeated once more to handle future risk situations.

## Summary

At the moment, there is a lack of effective treatment methods for clients in substance abuse treatment. The treatment for heroin addiction is characterized by substantial dropout of residential treatment and relapse to heroin use after a period of abstinence.

Research has shown that many substance dependent clients in (residential) treatment are disturbed by a strong desire for drugs (e.g., 'craving') when being confronted with drug related stimuli. When an ex-drug abuser who has been admitted to residential treatment for some time, returns to his or her familiar ambiance where drug use was common, it has often been reported that this person is 'surprised' by an intense desire to use drugs again. This is because this old ambiance is a "cue" which has repeatedly been associated with drug use, because in this setting drugs have been used repeatedly. Therefore the ambiance (the cue) has now become a predictor of drug use and can evoke strong reactions, such as craving to use the drugs but also physiological reactions can occur such as sweating, trembling and palpitation of the heart.

There are various types of drug related cues; 'external' cues (such as drug-related neighbourhoods, tin foil, money, certain music) or 'internal' cues (such as anger, grief, worrying, depressive mood states) which trigger the desire to use drugs. The subjective and physiological reactions to these cues are called cue reactivity.

In the treatment of substance dependent clients, emphasis is often focused on avoiding these drug-related cues, since they are able to evoke such strong reactions. This model of 'cue-avoidance' makes that many clients do not experience cue reactivity during their admission but when they re-enter the 'non-therapeutic' world, they can be surprised by intense reactions when confronted with drug-related stimuli.

Some studies have shown that cue reactivity is a predictor of relapse, the use of the substance after a period of abstinence.

Therefore, it seems illogical to adopt this model of cue-avoidance; drug-dependent clients will be confronted with drug-related stimuli one way or the other. It would be better to find a way to diminish the reaction towards these cues. One of the ways to do this is to expose individuals to these cues (which predicts drug use) and to subsequently adopt a different response, i.e., not using the drug. At first the cues will elicit cue reactivity but when this strategy is applied often, cues will loose their predictive value. The cues have now become to predict something else, i.e., not using the drugs and will have less impact on the client. During Cue Exposure Therapy (CET), this principle of

cue exposure with response prevention is performed in a systematic and structured manner. The therapist exposes the client to as many individualized drug-cues as possible, and repeats this until cue reactivity 'extincts' by means of Pavlovian deconditioning.

This thesis describes an effect study in which hundred-and-twenty-seven abstinent heroin dependent clients, admitted in residential treatment, were randomised to either nine session of CET (N=65) or placebo-psychotherapy (PPT, N=62). Cue reactivity and attentional bias to heroin-related stimuli were measured at baseline, post-therapy and at three-month follow-up measurement. The main hypothesis was that CET, through extinction of cue reactivity, would lead to less dropout from the residential treatment centre and lower relapse rates at follow-up.

Chapter 1 is an introduction where various theoretical models concerning CET are discussed such as the model of classical conditioning and theories about the origin of cue reactivity. Subsequently, cue reactivity among opiate dependent clients is discussed, and how in the present study it is attempted to reduce this reactivity through means of CET. Finally, a review is given describing the randomised studies which examined the efficacy of CET among (abstinent) substance dependent clients. There seems to be a lack of CET effect-studies, and often these studies are hampered by methodological limitations. For example, so far only one study examined the effect of CET among heroin dependent clients which included a control therapy and a follow-up measurement. Or, the studies designs are hampered by including a second intervention in addition to CET (mostly some kind of coping skills training). Such an addition makes it impossible to determine which element of which intervention caused treatment effects. It is concluded that up to today there is no evidence that CET is an effective intervention for the treatment of addictive disorders. Therefore, in the present study some limitations known from earlier studies are taken into account. This resulted in a randomised controlled study among (abstinent) heroin dependent clients, in which we examined the effect of 'basic' CET compared to placebo-psychotherapy.

In chapter 2, an outline of this thesis is given. The content of the chapters and their accompanying hypotheses are described.

In chapter 3 and 4, the concept of cue reactivity was examined. During baseline assessment, we measured whether participants indeed responded with cue reactivity as a reaction to heroin stimuli. To measure cue reactivity, we assessed participant's reactions to a video of a heroin user while simultaneously vaporizing heroin as an additional 'cue'. We found that cue reactivity was present but that the relation between self-reported cue reactivity (craving for heroin and mood) and physiological scores (skin conductance responses) was low or absent.

In chapter 3, a possible explanation for this finding is tested, that the mechanism of social desirability (in this case to provide the researchers with socially desirable answers) effects the relation between self-reported and physiological cue reactivity. We found a negative relationship between social desirability and self-reported craving and no relation with physiological reactivity. However, the hypothesis that social desirability influences the relation between self-reported and physiological cue reactivity could not be confirmed. Explanations for these findings are being discussed.

In chapter 4, predictors of cue reactivity are described and it is stated that individual differences in responses on drug cues are present. Predictors of 'instant' heroin craving and skin conductance responses to the heroin video were identified. We found no association between the two forms of reactivity and, even more, that they were predicted by different variables. The most important predictor of self-reported heroin craving was self-efficacy; the perceived ability to resist heroin in risk-situations. For skin conductance reactivity the most important predictors were years of heroin use and hostility.

Chapter 5 can be seen as the main chapter of this thesis, in which the effect of CET is described. Outcome measures concerning cue reactivity, dropout from the therapeutic centre and at least one time heroin use since post-treatment are described. We found that CET did not influence self-reported mood, craving for heroin or self-efficacy. What we did find was an effect of CET on skin conductance responses compared to placebo-psychotherapy. We therefore conclude that the hypothesis that CET extinguishes cue reactivity is partly confirmed, at least in its ability to extinct a physiological reaction to heroin stimuli. Contrary to our hypothesis we found that CET led to higher dropout from the therapeutic centre and higher relapse rates compared to placebo-psychotherapy. Relapse was defined as 'at least one time heroin use' during follow up. We defined

participants whom we were unable to locate at follow up as 'relapsed'. This resulted in a dropout percentage of 22.6% in the PPT group vs. 50.8% in the CET group. The relapse percentage was 12.9% in the PPT group vs. 40.0% in the CET group. In addition, we found that these significantly different dropout and relapse rates were unrelated to changes in cue reactivity (mood, craving or skin conductance responses) or self-efficacy. These unexpected findings are further discussed and retrospectively some possible explanations are mentioned. This is the first study that shows that CET might have detrimental effects in a population of heroin-dependent clients in residential treatment.

In chapter 6, the psychological mechanism of attentional bias is studied, the selective attention of drug-addicts to drugs and drug-related stimuli.

It is known from earlier studies that abstinent drug dependent individuals show an attentional bias to drug related words compared to neutral words during a so-called stroop-task. This was confirmed in the present study, we found that participants were slower in responding (i.e., in naming the colour of in which the word was presented) to heroin-related words as opposed to neutral words. Our hypothesis was that attentional bias could be seen as a form of cue reactivity and could therefore be diminished through CET. To test this, we examined Stroop-data before and after treatment between groups. Our hypothesis could not be confirmed, compared to our PPT, no effect was shown from CET on attentional bias. A possible explanation for this finding is that stimuli associated with 'approach' or 'wanting' are more difficult to extinct than are stimuli associated with 'avoidance' such as fear-related stimuli. We found baseline attentional bias to be a predictor of relapse at follow-up, also when controlling for pre-treatment self-reported heroin craving. This is in line with attentional bias studies among smokers and alcoholics, but this is the first study which shows that attentional bias is a predictor of relapse among heroin dependent clients. The idea that attentional bias taps an important aspect of addiction is confirmed.

The last chapter, chapter 7 is an overview of the present thesis. Our main results are being explored further and the future of CET as a potentially effective treatment in the addiction field is discussed.

Several explanations are being explored why in our population CET was not effective in reducing subjective cue reactivity (mood, heroin craving, self-efficacy). A possibility is that while for anxiety disorders through CET a number of irrational cognitions are being

adjusted, in addictive disorders cognitions often have a rational nature and are therefore not necessarily changed. It is concluded that CET is partly effective in extinguishing cue reactivity, however this does not imply that it is an effective treatment in clinical practice. The higher dropout- and relapse rates may suggest that through CET a paradoxical sensitisation effect occurred which enhanced vulnerability of participants in our population.

However, this is only one of the retrospective explanations for a completely unexpected finding in an effect study. The bottom line is that we do not know exactly why we found an opposite effect of CET and therefore emphasize, both on clinical and ethical grounds, to be careful in using this intervention as long as it is unclear which unintended effects it might have.

# Samenvatting

Op het moment zijn er voor mensen met een verslaving aan heroïne weinig effectieve behandelmethoden. De behandeling voor heroïneverslaving wordt gekenmerkt door een aanzienlijke uitval uit residentiele behandeling en veelal vallen mensen terug in gebruik na een tijd abstinent geweest te zijn.

Uit onderzoek is gebleken dat veel ex-verslaafden in (klinische) behandeling last hebben van een sterk verlangen naar drugs, oftewel craving, wanneer ze geconfronteerd worden met druggerelateerde stimuli. Het kan bijvoorbeeld zo zijn dat als een ex-verslaafde na een tijd opgenomen geweest te zijn weer terugkomt in zijn oude omgeving waarin hij gebruikte, ineens overvallen wordt door een intense drang om weer te gebruiken. De oude vertrouwde omgeving is dan een "cue" die geassocieerd is met het gebruiken van heroïne, in die omgeving is immers herhaaldelijk heroïne gebruikt. Daardoor is die omgeving (de cue) een voorspeller geworden van heroïnegebruik en kan deze cue sterke reacties teweegbrengen zoals trek om te gebruiken maar ook lichamelijke reacties zoals zweten, trillen en hartkloppingen. Cues kunnen vele vormen aannemen; het kunnen stimuli buiten de persoon zijn (zoals gebruikersbuurten, een rol aluminiumfolie, het zien van geld, bepaalde muziek) of stimuli 'binnen' de persoon (zoals woede, verdriet, piekeren, depressieve buien) die aanleiding geven tot het verlangen om te gebruiken.

De subjectieve en fysiologische reacties die deze cues oproepen noemen we cue-reactiviteit. In de behandelsettings voor verslaafden wordt de nadruk vooral gelegd op het vermijden van druggerelateerde cues omdat deze zulke heftige reacties op kunnen roepen. Dit model van cuevermijding leidt ertoe dat veel ex-verslaafden tijdens hun opname geen last hebben van cue reactiviteit maar dat ze wanneer ze weer in de "niet-therapeutische" wereld komen, ze als het ware overvallen worden door de confrontatie met druggerelateerde cues die heftige reacties oproepen. Sommige studies hebben aangetoond dat cue-reactiviteit kan leiden tot terugval, het weer opnieuw gaan gebruiken van het middel.

Het lijkt er dus op dat het niet verstandig is om volgens dit cue-vermijdingsmodel te werk te gaan, mensen die verslaafd zijn geweest zullen ook na een tijd abstinent te zijn geweest geconfronteerd worden met meerdere cues. Beter zou het zijn om een manier te vinden om de reactie op die cues te verminderen. Een van de manieren hiervoor is om mensen bloot te stellen aan deze cues (die druggebruik voorspellen) en om hier

vervolgens een andere gebeurtenis op te laten volgen namelijk het niet gebruiken van het middel. Wanneer dit vaak genoeg gedaan wordt zullen de cues in eerste instantie cue reactiviteit uitlokken maar uiteindelijk verliezen deze cues hun voorspellende waarde. De cues voorspellen nu iets anders, namelijk niet gebruiken en zullen minder impact hebben op de cliënt. Tijdens Cue Exposure Therapie (CET) wordt dit principe van cue-confrontatie met daaropvolgend responspreventie op systematische en gestructureerde wijze toegepast. De therapeut stelt de cliënt bloot aan zoveel mogelijk persoonlijke druggerelateerde cues, net zovaak totdat reactiviteit op de cues 'uitdooft'.

Dit proefschrift is een beschrijving van een effect studie waarbij honderdzevenentwintig abstinente heroïneverslaafden, opgenomen in een residentiel setting, werden toegewezen aan ofwel negen sessies CET (N=65) of placebo-psychotherapie (PPT, N=62). Hierbij werd gekeken naar het verschil in cue reactiviteit en selectieve aandacht voor heroïnegerelateerde stimuli bij aanvang van het onderzoek, na de therapieën en tijdens een follow-up na drie maanden. De verwachting was dat CET, door het verminderen van cue reactiviteit, een effectieve behandeling zou zijn in het verminderen van uitval uit de residentiele setting en het verminderen van de kans op terugval in heroïnegebruik.

Hoofdstuk 1 is een inleidend hoofdstuk waar een aantal theoretische modellen m.b.t. CET besproken worden zoals het model van klassieke conditionering en theorieën over het ontstaan van cue reactiviteit. Vervolgens wordt ingegaan op wat er bekend is over cue reactiviteit bij opiaatverslaafden en hoe in de huidige studie getracht is deze reactiviteit te verminderen door het aanbieden van CET. Als laatste wordt er een overzicht gegeven van gerandomiseerde studies die de effectiviteit van CET hebben getoetst bij (abstinente) verslaafden. Er zijn maar weinig studies gedaan naar het effect van CET bij verslavingsproblematiek en de studies die er gedaan zijn, hebben een aantal methodologische tekortkomingen. Tot nu toe is er bijvoorbeeld maar 1 studie gedaan naar het effect van CET bij heroïne verslaving welke een controlegroep en een follow-up meting bevatte. Of worden er naast de CET ook andere interventies in de studie designs getoetst (meestal een vorm van coping-skills training) zodat achteraf het effect van de afzonderlijke onderdelen niet meer goed onderscheiden kan worden. Geconcludeerd wordt dat tot nu toe niet is aangetoond dat CET een effectieve therapie is voor de behandeling van verslavingsproblematiek.

Daarom is er in de huidige effectstudie rekening gehouden met een aantal knelpunten die naar voren kwamen in vorige CET studies. Dit resulteerde in een

gerandomiseerde studie waarin we het effect van 'basis' CET vergeleken ten opzichte van een placebo-psychotherapie bij (abstinente) heroine-afhankelijke cliënten.

Hoofdstuk 2 geeft een overzicht van de opzet van dit proefschrift. Er wordt een korte beschrijving gegeven van de afzonderlijke hoofdstukken en de bijbehorende vraagstellingen.

In hoofdstuk 3 en 4 wordt het begrip cue reactiviteit onder de loep genomen. Tijdens de baseline meting, voor aanvang van de interventies, is er gemeten of deelnemers daadwerkelijk cue reactiviteit vertoonden als reactie heroïnestimuli. Als maat voor cue-reactiviteit hebben we de reactie van deelnemers op een video van een heroïnegebruiker gemeten terwijl er tegelijkertijd heroïne werd verbrand als additionele 'cue'. Er werd gevonden dat er inderdaad sprake was van cue-reactiviteit, maar dat er maar weinig tot geen samenhang was tussen zelfgerapporteerde scores (trek in heroïne en stemming) en fysiologische scores (huidgeleidingsactiviteit).

In hoofdstuk 3 wordt een mogelijke verklaring voor dit gegeven getoetst, namelijk dat het mechanisme van sociale wenselijkheid (in dit geval de neiging om de onderzoekers sociaal wenselijke antwoorden te verschaffen) de relatie tussen zelfgerapporteerde en fysiologische reactiviteit beïnvloedt. Er werd een negatieve samenhang gevonden tussen sociale wenselijkheid en zelfrapportage, en geen samenhang met fysiologische reactiviteit. Echter, de hypothese dat sociale wenselijkheid van invloed is op de relatie tussen zelfgerapporteerde en fysiologische cue reactiviteit werd niet bevestigd. Verklaringen en implicaties m.b.t. deze bevindingen worden in de discussie besproken.

Hoofdstuk 4 beschrijft voorspellers van cue reactiviteit en stelt dat er individuele variatie is in het reageren op druggerelateerde cues. Gekeken is naar voorspellers van 'acute' heroïne craving en huidgeleidingsresponsen als reactie op de heroïnevideo. Er werd gevonden dat deze twee reactiviteitsmaten niet met elkaar samenhingen en sterker nog, voorspeld werden door verschillende variabelen. De belangrijkste voorspeller van zelfgerapporteerde heroïne craving was self-efficacy; hoe zeker mensen van zichzelf zijn om heroïne te kunnen weerstaan in risicosituaties. Er was een negatieve samenhang tussen deze variabelen. Voor huidgeleidingactiviteit waren de belangrijkste voorspellers aantal jaren heroïnegebruik en hostiliteit.

Hoofdstuk 5 kan als de kern van dit proefschrift beschouwd worden, waarin het effect van CET beschreven wordt. De uitkomsten m.b.t. cue reactiviteit, uitval uit de residentiele setting en ten minste een eenmalige terugval in heroïnegebruik worden hier beschreven. Het blijkt dat CET geen effect heeft gehad op zelfgerapporteerde stemming, trek in heroïne of self-efficacy. Wel was er een effect op huidgeleidingsresponsen na CET ten opzichte van PPT. Hierdoor wordt geconcludeerd dat de theoretische achtergrond van CET gedeeltelijk klopt, namelijk dat CET werkzaam is in het uitdoven van cue reactiviteit, althans op een fysiologische maat. Tegengesteld aan onze verwachtingen vonden we dat, vergeleken met onze placebo-psychotherapie, de deelnemers na CET eerder de residentiele setting verlieten en ook eerder waren teruggevallen in ten minste eenmalig heroïnegebruik ten tijde van de follow-up. In de analyses hebben we de deelnemers die onvindbaar waren ten tijde van de follow-up gedefinieerd als 'teruggevallen'. Dit resulteerde in een uitval percentage van 22.6% in de controlegroep tegenover 50.8% in de CET groep. Voor terugval in heroïnegebruik was dit 12.9% in de controlegroep ten opzichte van 40.0% in de CET groep. We vonden bovendien dat deze significant verschillende uitval en terugvalpercentages niet voorspeld werden door cue reactiviteit (stemming, trek, of huidgeleidingsresponsen) of door self-efficacy. Deze zeer onverwachte effecten worden verder besproken in de discussie en retrospectief worden een aantal mogelijke verklaringen genoemd. Dit is het eerste onderzoek dat aantoont dat Cue Exposure Therapie wellicht schadelijk kan zijn voor heroïneafhankelijke cliënten in een residentiele setting.

In hoofdstuk 6 is gekeken naar het psychologische mechanisme van 'attentional bias', wat zich onder verslaafden uit in selectieve aandacht voor drugs en druggerelateerde stimuli. Uit eerder onderzoek is gebleken dat abstinente verslaafden attentional bias vertonen naar heroïnegerelateerde woorden ten opzichte van 'neutrale woorden' wanneer dit gemeten wordt met een zogenaamde 'stroop-taak'. Dit werd bevestigd in de huidige studie waarin gevonden werd dat deelnemers langere reactietijden vertonen in het benoemen van de kleur van een heroine-gerelateerd woord ten opzichte van een neutraal woord. Onze oorspronkelijke hypothese was dat attentional bias mogelijk als een vorm van cue-reactiviteit gezien kan worden en daardoor ook uitgedoofd zou kunnen worden door CET. Om dit te testen vergeleken we de Stroop-scores voor en na de behandeling tussen de groepen met een 'repeated measures' analyse. Onze hypothese kon niet bevestigd worden, er werd ten opzichte van de controlegroep geen effect van CET op attentional bias waargenomen. Dit heeft

mogelijk te maken met het feit dat stimuli geassocieerd met 'aantrekkingskracht' zoals drugsgerelateerde stimuli, moeilijker te beïnvloeden zijn dan stimuli geassocieerd met 'vermijding' zoals angstgerelateerde stimuli. Wel bleek dat de attentional bias van deelnemers bij aanvang van het onderzoek een voorspeller was van terugval ten tijde van de follow-up, ook wanneer gecontroleerd wordt voor zelfgerapporteerde craving. Dit is in overeenstemming met wat gevonden is in eerdere attentional bias studies naar alcohol-en rookverslaving maar is de eerste studie die een voorspellend effect van attentional bias op relapse vindt onder heroïne afhankelijke cliënten. Het idee wordt bevestigd dat attentional bias een belangrijk aspect is van verslaving.

Het laatste hoofdstuk, hoofdstuk 7 is een overzicht van dit proefschrift. Er wordt wat dieper ingegaan op de hoofdbevindingen en de toekomst van Cue Exposure Therapie als behandeling voor verslavingsproblematiek wordt besproken.

Een aantal verklaringen worden gezocht voor het feit dat in onze doelgroep CET geen effect heeft gehad op de subjectieve beleving van cue reactiviteit (stemming, trek in heroïne, self-efficacy). Een mogelijkheid is dat bij CET bij angststoornissen er bijkomstig een aantal irrationele cognities veranderd worden terwijl de cognities bij verslaving vaak reëel van aard zijn en deze dus niet logischerwijs veranderen.

Er wordt geconcludeerd dat CET gedeeltelijk effectief is in het uitdoven van cue reactiviteit, maar dat dit geenszins impliceert dat dit een effectieve behandeling in de praktijk is. De hogere uitval en terugval percentages kunnen er op wijzen dat er door CET mogelijk een paradoxaal sensitisatie effect heeft plaatsgevonden wat de kwetsbaarheid van de mensen in onze doelgroep heeft versterkt. Dit is echter een van de retrospectieve verklaringen, naar aanleiding van een geheel onverwachte uitkomst van een effect studie. Waar het op neerkomt is dat we niet weten waarom CET een tegengesteld effect heeft gehad en benadrukken vanuit klinisch en ethisch oogpunt voorzichtig te zijn met deze interventie zolang we niet weten welke onverwachte effecten deze teweeg kan brengen.

# Dankwoord

Tijdens het werken aan dit proefschrift deed ik mijn eerste stappen in de onderzoekswereld. Dit viel niet altijd mee, en gedurende dit proces heb ik dan ook vele mensen om hulp gevraagd, op allerlei wijze lastig gevallen, als praatpaal of als inspiratiebron gebruikt. En deze mensen waren er ook, als er weer eens iets misging, iets kapot ging, ik het niet meer zag zitten en ook wanneer het leuk was. Daarvoor wil ik de volgende mensen bedanken.

Ik wil beginnen met Linda Kroon, jij startte met het onderzoek en hebt me geleerd wat Cue Exposure Therapie is. Ik wil je bedanken voor het werk wat je hebt verricht en ben benieuwd wat je vindt van het eindresultaat.

Mijn promotor, Wim van den Brink, ben ik met name dankbaar voor het scheppen van duidelijkheid in toestanden van chaos; als we een afspraak hadden gehad wist ik daarna weer waar ik ook al weer mee bezig was en had ik weer inspiratie om verder te gaan.

Vincent Hendriks, jij hebt me het zetje gegeven wat ik nodig had om onderzoek te gaan doen met mijn ‘behandelaarmentaliteit’. Al waren we het niet altijd met elkaar eens, achteraf ben ik hier heel blij om en kan ik zeggen dat ik er erg veel van heb geleerd, bedankt hiervoor.

Ingmar Franken, jij was de meeste tijd mijn directe begeleider en hebt hierdoor misschien wel het meeste met mij te stellen gehad. Omdat we ook vrienden geworden zijn, was de drempel voor mij laag om al mijn zogenaamd ‘praktische’ vragen en ongenuanceerde meningen op jou af te vuren wanneer ik dat nodig achtte. Echter, jij bleef hier over het algemeen opmerkelijk rustig onder en hebt me ontzettend vooruit geholpen, dankjewel hiervoor.

Peter Blanken, ook jou wil ik bedanken voor je begeleiding en geduld. Tijdens alle uren verwerking van de fysiologische gegevens bijvoorbeeld, wanneer ik op het punt stond de computer van ergernis uit het raam te gooien was jij altijd weer een relativerende factor en dat heeft me goedgedaan.

Anneke Posthumus, jij verrichtte de eerste tijd van het onderzoek alle metingen en bent hierdoor een grote steun voor me geweest. Ik vond het heel prettig en vooral gezellig om met je samen te werken. Toen jij en Ingmar ongeveer tegelijkertijd

vertrokken, zag ik het even niet meer zitten maar gelukkig kreeg ik er net zulke geweldige collegae voor in de plaats.

Te beginnen met Eveline de Wilde, jij nam de metingen van Anneke over en al snel vonden wij elkaar, in eerste instantie in de gedeelde liefde voor onze cliënten en later in nog heel veel meer. Ik hoop dat we behalve als vrienden ook nog eens onze kracht als team in de praktijk kunnen gaan brengen.

Hetzelfde geldt voor Michelle Dujardin, tijdens onze samenwerking kwamen we erachter dat 'Durism' het concept van de toekomst is. Je hebt me vanaf het begin bijgestaan bij alle leuke en rottige details van mijn PARC-carriere en we hebben hier altijd ontzettend om kunnen lachen, dankjewel.

Margreet Kerkmeer, behalve humor heb je ook een enorme statistische- en 'feitjes' kennis, waar ik ten aller tijden gebruik van mocht maken, bedankt hiervoor.

Ook Tamara van Batenburg-Eddes wil ik bedanken voor de hulp en gezellige samenwerking.

Soms komen er mensen op je pad die je, zonder het zelf te weten, inspireren om de richting op te gaan waar je moet zijn. In deze context wil ik bedanken: Philip Kroonenberg, Michel Odufrè en Kees Korrelboom voor wiens werkwijze ik een enorm respect heb.

Verder wil ik nog bedanken voor de prettige samenwerking: Anne van Maastricht, Ghalied Barsatie, Tony Bloemendaal, Bep de Lange, Hans van Nes, Peter Dercksen en Ron Strijaards.

En natuurlijk de cliënten die zo dapper als proefpersoon hebben deelgenomen aan dit onderzoek, ik heb ontzettend veel geleerd van het luisteren naar al jullie verhalen.

Dan mijn vrienden bij wie ik altijd terecht kon als dat nodig was.

Marleen, Liesbeth, Natasja,

Pleun, Sacha, Bart, Femke, Marieke.

En ook in deze context weer Michelle, Eef, Ingmar en Margreet.

Lieve Sander, dankjewel voor de kunst op de voorkant maar vooral voor al je liefde.

Papa en Opa, mijn eigenwijsheid en doorzettingsvermogen heb ik van jullie en dat heb ik goed kunnen gebruiken, bedankt voor alles wat jullie voor me gedaan hebben.

# Curriculum vitae

Marlies Marissen werd op 15 September 1978 in Utrecht geboren. In 1997 begon zij met haar studie Psychologie te Leiden, alwaar zij in februari 2001 haar doctoraal behaalde in de Klinische- en Gezondheidspsychologie. Tijdens het laatste jaar van haar studie kreeg ze de gelegenheid werkervaring op te doen als psycholoog middels de uitvoering van Cue Exposure behandelingen bij het Parnassia Addiction Research Centre. Vervolgens werd zij in mei 2001 aangesteld als promovenda op ditzelfde onderzoek. Deze aanstelling mondde uit in het schrijven van dit proefschrift. Sinds november 2004 heeft zij een aanstelling als psycholoog bij de afdeling Persoonlijkheidsproblematiek van Parnassia te Den Haag alwaar zij therapeutische- en onderzoekstaken verricht.

Steef 28-04-03

No more victim

I used to be a victim
I used to be a liar
I used to be a drunk
I used to be a junk

I’m starting to be a fighter
I’m starting to tell the truth
I’m starting to get sober
I’m getting of the drugs

7 weeks later and still the fight goes on
7 weeks and I’m telling more about my life
7 weeks and still I don’t drink
7 weeks and the monkey is still on my back

Where will I be in a year
Will I be fighting
Will I still tell the truth
Will I still don’t drink
Will I still be clean

I hope I will
I hope I’ll be happy
I hope I will be glad
I hope I will be loved
I hope I will be proud