Cognitive and neuropsychopharmacological processes in human drug craving
Franken, I.H.A.

Citation for published version (APA):

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

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

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

Download date: 28 Dec 2018
Summary

Heroin dependence is an important public health problem that creates substantial suffering for the patient, the family and society at large. Treatment is largely symptomatic and relatively little is known about the underlying mechanisms of onset and relapse. One of the characteristic experiences in addictive behavior is craving (or urges). Craving refers to the desire to experience the effect of a previously experienced psychoactive substance. This craving plays a major role in addictive behaviors and is believed to contribute to loss of control and relapse after abstinence. For theoretical and clinical progress it is important to find a valid model of craving. Recently, animal research revealed both psychological and biological mechanisms of craving, however, less effort has been put in integrating these models and applying the knowledge in human studies.

Most animal models of addiction contain the concept of incentive motivational processes. Incentive motivation can be defined as a cognitive and affective state triggered by stimuli associated with the perception of unconditioned stimuli. According to the incentive motivation model, and supported by a host of empirical evidence, drug-related stimuli are able to elicit classically conditioned responses in drug addicts, both physiologically and subjectively (e.g. "craving"). The classical conditioning model of substance use posits that previously neutral environmental stimuli acquire the ability to elicit conditioned drug responses. When the environmental stimuli are repeatedly presented to the subject, and paired with the substance use, these stimuli are able to elicit a conditioned response (craving and physiological responses). In most current conceptualizations of drug dependence, this cue-elicited subjective craving is regarded as a central phenomenon, contributing to the continuation of drug use and the occurrence of relapse.

In human models of addiction, cognitive factors such as memory processes, expectancies, and attentional processes are believed to play an important role in the process of relapse. At the moment, one of the major theoretical and research challenges in the addiction field is to gain knowledge on the neurobiological and cognitive processes behind the classically conditioned relation between drug stimulus and craving in humans.

In the present thesis, the role of cognitive processing in craving is studied from an integrated perspective that includes neuropsychopharmacological and psychological theories. A model of human drug craving is proposed which attempts to explain craving and drug seeking in humans through the psychological mechanism of "attentional bias". According to this model, cognitive processes mediate between drug stimuli and the subject's response to these stimuli and subsequent behavioral responses (e.g. drug use, relapse). Furthermore, the model predicts that a conditioned drug stimulus produces an increase in dopamine levels in the corticostriatal circuit, in particular the anterior cingulate gyrus, amygdala, and nucleus accumbens, which in turn serves to draw the subject's attention towards a perceived drug stimulus. This process results in preparation for drug approach and a hyperattentive state towards drug-related stimuli that, ultimately, promotes further craving and relapse.

In chapter 1, cognitive and neuropsychopharmacological processes in craving are discussed and an integrative model is proposed. Furthermore, support for this model is reviewed from both the psychopharmacological and psychological point of view.

In chapter 2, an outline addressing which aspects of the model will be tested is provided and the several experimental paradigms are explained.

In chapter 3, the psychometric properties of two heroin craving questionnaires was examined. This validation study was necessary because no valid heroin craving instruments were available. These instruments are the "Desire for Drug Questionnaire" (DDQ) and the "Obsessive Compulsive Drug Use Scale" (OCDUS). The DDQ measures three factors
of "instant" craving: desire and intention, negative reinforcement, and control. The OCDUS measures three factors of "chronic" craving (during the past week): thoughts about heroin and interference, desire and control, and resistance to thoughts and intention. Subjects were 102 Dutch patients who were currently in treatment for drug dependency. In contrast to the factor structure of the DDQ, the factor structure of the OCDUS scales did not resemble the theoretically proposed scales. As a result of this, the scales of the OCDUS were adapted in order to improve the psychometric properties. All resulting scales of both the DDQ and the OCDUS have fair to good reliability and concurrent validity. In addition, both questionnaires are easy to administer in clinical populations and are reliable instruments for use in clinical trials on pharmacological or psychotherapeutic interventions aimed at reducing craving and relapse. Further study on the concurrent and predictive validity of the OCDUS and the DDQ is needed. Studies that address the correlation between these questionnaires and physiological measures of cue reactivity will contribute to their validation.

In chapter 4, the hypothesis that selective processing of drug cues may be involved in drug craving was investigated. In order to study this role of processing bias in an abnormal motivational system, the attentional bias for drug related stimuli was studied in a heroin dependent population. Heroin dependent participants (n=21) and control participants (n=30) performed a supra- and subliminal heroin Stroop task and heroin craving was assessed. It was found that heroin dependent participants showed considerable attentional bias for supraliminal heroin cues. However, there was no evidence for a preattentive bias on the subliminal cues. Reaction time on heroin cues was significantly predicted by heroin craving-levels. This study shows for the first time that attentional processes in heroin dependence are biased. Heroin dependent patients process heroin related cues selectively, that is, more attentional resources are directed towards heroin cues compared to neutral cues. The reaction time on drug related cues was found to be correlated with self-reported craving for heroin. Although no evidence for the existence of a preattentional bias on subliminally presented stimuli was found, for one of the craving measures a significant relation was observed with reaction times on subliminal presented drug cues. A tentative explanation for this finding may be that a subgroup of heroin addicts (i.e. the high cravers) displays also a preattentional bias for drug related cues.

In chapter 5, the relation between craving, obsessive thoughts about cocaine, experienced control and attentional bias for cocaine related words was investigated. Sixteen abstinent cocaine abuse patients participated in a reaction time experiment in order to measure the ability of subjects to shift their attention away from cocaine related words. Post-experiment craving was found to be positively correlated with reaction times on drug related cues, and not to reaction times on neutral cues. Furthermore, obsessive thoughts about cocaine use and the experienced cocaine use control in the week before the experiment were stronger correlated with reaction times on drug cues than with post-experiment craving. Attentional bias for drug cues was more present in patients with higher score on obsessive cocaine thoughts and higher craving scores. For the first time, this study shows a relation between obsessive thoughts about cocaine, experienced control, craving and attentional bias operationalized as the ability to disengage from cocaine related cues. This implicates that, in a cocaine abuse patient population, craving levels are related to information processing mechanisms. Furthermore the study provides some indication that this attentional bias is an automatic process.

In chapter 6, the relation between Gray's personality dimensions behavioral inhibition system (BIS) and behavioral approach system (BAS) and cue elicited alcohol craving was studied. In this study participated both alcoholics and social drinkers. It was found that BAS sensitivity was related to both desire and negative reinforcement aspects of alcohol
craving, and that drinking history was related to both control and negative reinforcement aspects of craving. Subjects with high BAS-drive scores experienced significant more strong desires, intentions to drink alcohol, and negative reinforcement craving during exposure to alcohol related cues than subjects with low BAS-drive scores. The findings are supportive for the personality theory of Gray, which predicts that high BAS activity is positively correlated with increased desire for alcohol drinking. From neurobiological perspective, the present findings are in line with the theory of Depue & Collins who suggest that the personality factor of extraversion (which is closely related to BAS) is explained by variability in the sensitivity to incentive stimuli and DA agonists (such as alcohol). Persons with high dopamine transmission from the ventral tegmental area (VTA) to the nucleus accumbens (NA), i.e. extraverts, are expected to have enhanced responsivity to incentive stimuli (such as alcohol cues). It is known for many years that almost all addictive drugs (including alcohol) and predictors of drug intake (conditioned incentive stimuli) activate the same VTA-NA dopamine transmission. Accordingly, the observed relation between desire aspects of alcohol craving in response to incentive stimuli and the BAS sensitivity may possibly be explained by activation of the same neurobiological dopamine transmission pathway.

In chapter 7, the hypothesis was tested that abstinent alcoholics would demonstrate enhanced memory for alcohol-related pictures (memory bias) compared to non-alcoholic drinkers. In addition, it was hypothesized that there would be a positive relation between alcohol craving and this memory bias. The cognitive processing of alcohol cues was compared to general incentive cues (food) and neutral cues in a group of alcoholics (n=26) and non-alcoholic (light) drinkers (n=24). Alcoholics showed enhanced memory for alcohol cues compared to neutral or general incentive cues. Moreover, the magnitude of this bias was positively correlated with alcohol craving. This study provides evidence for the presence of a memory bias for alcohol cues in alcoholics. This memory bias possibly results in enhanced alcohol craving. The present findings are in line with neurobiological accounts of addiction. Frequent alcohol use may change neural circuits involved in memory. Previous studies have demonstrated that the memory circuits of cocaine addicts are activated during the experience of cocaine craving. The current finding that memory bias is related to increased craving supports White's theory that memory processes are essential to the analysis of changes in behavior produced by addictive drugs.

In chapter 8, EEG power and coherence measures of 18 abstinent heroin dependent subjects with 12 healthy control subjects were compared. Electroencephalogram (EEG) power and coherence analysis are two important tools for examining the effects of drugs on brain function. EEG power refers to the background cortical activity in a predefined frequency band. EEG coherence analysis is a technique that focuses on the pairwise correlations of power spectra obtained from different electrode leads. It measures the functional interactions between brain areas in different frequency bands. Within the heroin group, associations between heroin use in the past, heroin craving and these EEG measures were studied. The results show that heroin dependent subjects have increased relative beta2 power and increased left intra-hemispheric gamma coherence compared to control subjects. Furthermore, coherence measures showed correlations with clinical variables. These EEG abnormalities may reflect underlying changes in brain function due to long-term drug use. These findings indicate that, in addition to power analysis, coherence analysis may be a useful tool for studying substance-induced abnormalities of the functioning of the brain. Furthermore, the findings suggest that coherence measures are associated with drug use variables and clinical variables, which implies that coherence measures reflect state related conditions such as heroin craving. More research is needed that addresses the usefulness of EEG coherence measures as indicators of drug craving.
In chapter 9, event-related brain potentials (ERPs) and the cue modulated startle response (CMSR) were evaluated as indicators for cocaine craving. Twenty-one abstinent cocaine dependent subjects were divided in a high and low cravers group based on the median split of self-reported craving scores. ERPs and CMSR were measured while subjects watched neutral, pleasant, unpleasant, and cocaine related pictures. Overall, it was found that the cocaine dependent subjects showed augmented slow-positive waves (SPWs) of the ERP on the cocaine pictures, compared to neutral pictures. Furthermore, it was found that these cue-elicited SPWs were positively correlated with self-reported cocaine craving. Specifically, on the cocaine cues the high craving group showed more positivity on the late positive wave reactivity than low cravers. In contrast to the ERP measures, CMSR did not differentiate between cocaine pictures and neutral pictures. In addition, no differences between the low- and high cravers on the CMSR measure were found. The present results show that the evoked-potentials paradigm provides promising results to study cue-elicited craving. Of the two studied physiological indicators of cocaine craving, the ERP (sustained) slow positive wave (SPW) turned out to provide the most unambiguous measure for cocaine craving. Since the SPW results did show an enhanced positivity of the wave on cocaine cues, it can be concluded that drug related stimuli do not only facilitate craving, but also have attention grabbing properties. This finding is supportive for theories describing addiction in general, and craving in particular, as connected with an alteration in attention.

In chapter 10, Event Related Potentials (ERPs) are used to investigate heroin related visual information processing. Neutral and heroin related pictures were presented to 19 male abstinent heroin dependent patients and 14 male healthy controls. Patients exhibited larger Slow Positive Wave (SPW) components of the ERP on heroin related pictures than on neutral pictures. Within healthy control subjects there was no difference on the SPW between neutral and heroin pictures. Within heroin dependent patients, mean SPW response to heroin pictures was correlated with post-experiment craving. This study provides neurophysiological support for the hypothesis that information processing of drug-related information is abnormal in heroin dependent patients. The finding that the Slow Wave to heroin pictures is greatly enhanced in heroin dependent patients suggests that these heroin cues are selected by the brain for sustained attentive processing. This is in accordance with the Incentive-Sensitization Theory of Robinson & Berridge, who claim that classically conditioned drug related stimuli have acquired attention-grabbing properties. The present study shows that this enhanced attentional processing sustains during at least a period of 6 seconds. Although the present study design does not allow for causality speculation, it is conceivable that this prolonged processing bias results in increased craving. Although the reactivity of the Slow Waves was in the hypothesized direction, we failed to find any differences between the two groups on the earlier (<400 ms) ERP components.

In chapter 11, the hypothesis that enhanced attention for heroin cues is mediated by the dopaminergic system using a haloperidol as dopamine-antagonist was tested. In a double blind, randomized crossover design, 18 detoxified heroin dependent patients received a single oral dose of haloperidol 2 mg and placebo. Patients performed an Emotional Stroop task under both conditions. In the haloperidol condition, patients showed less attentional bias than in the placebo condition. However, no effect on subjective craving was found. The hypothesis that haloperidol would reduce attentional bias in heroin dependent patients suggesting an important role for dopamine in this mechanism underlying drug addiction was only partly supported: haloperidol significantly reduced reaction times of drug related cues and not of neutral cues, but the interaction terms of Word Type by Condition was not significant (probably due to substantial reductions in the reaction times.
to both drug related and neutral cues). Overall selective attention was improved by haloperidol compared to placebo. Preliminary support was found for the hypothesis that the enhanced attention for drug related cues, which is present in drug dependent patients, is dopaminergic mediated. This support is consistent with the "Incentive-Sensitization" theory that claims that dopamine triggers the brain's attention towards motivationally significant stimuli.

Chapter 12, a concluding chapter, an overview of the status of the model was provided by discussing the results of the empirical studies as described in the previous chapters. Furthermore, future studies were proposed that should address the remaining issues that are not studied or that elaborate the preliminary findings of this thesis. Overall, it can be concluded that an attentional bias for drug related cues is present in different drug dependencies. Although the present studies shed some light on the pharmacological and neurophysiological underpinnings of this attentional bias, further studies should address this topic using brain-imaging techniques.