English summary

Substance use disorder (SUD) is considered as a chronic brain disorder, which is characterized by a continuation of compulsive drug taking even in the presence of severe negative side-effects. Heroin use disorder is one of the most harmful addictions due to the high mortality as a consequence of drug-specific and drug-related mortality. The current treatment of heroin use disorder is mainly focussed on harm reduction and prevention, instead of recovery from the addiction. As a consequence, prevalence of stable abstinence from opioid use is low resulting in a large burden for health care, society and the economy. Despite currently available treatments prevalence of stable abstinence from opioid use is low. Deep brain stimulation (DBS) is a potential new method for treatment-resistant patients. This neurosurgical procedure involves implanting electrodes in the brain which deliver electrical pulses to a specific brain target. DBS is already available for the treatment of Parkinson’s disease. Currently, DBS is investigated as a potential therapy for treatment-resistant patients suffering from psychiatric disorders such as obsessive-compulsive disorder (OCD) and SUD. The aim of this thesis was to explore the effects of DBS on different aspects of heroin taking and seeking using an animal model of heroin use disorder. In addition, we also studied the effects of DBS on distinct forms of impulsive behaviour, because a lack of impulse control is known to be an important facet of multiple psychiatric disorders for which DBS is currently investigated, including substance dependence.

Substance use disorder

Different animal models have been developed to study the underlying mechanisms of SUD. An extensive overview of the animal models and their translational value is given in chapter 2. The drug self-administration model is used for this thesis. In this model, rats are trained press a lever or to make a nose poke which results in an intravenous injection of heroin. Heroin delivery is accompanied by presentation of a light or sound cue. These stimuli have no motivational value in itself, but become associated with the rewarding effects of the drug after repeated presentation. This is comparable to the human situation, where a heroin addicted patient associates tools for heroin use with the effect of heroin. This model is also used to simulate motivational aspects of heroin taking by progressively increasing the number of responses required to obtain a single heroin injection. The highest ratio reached is an indication for the motivation to obtain a single heroin injection. Thirdly, this model is used to simulate relapse after a period of abstinence. This is achieved by exposing rats to the stimuli previously associated with heroin, without receiving heroin. In addition to conditioned stimuli, stress or an injection
with heroin can also be used to introduce relapse. These factors are also known to induce craving and relapse in addicted patients.

Besides a description of the animal models for addiction, an extensive review of the brain regions involved in SUD is given in chapter 2. Drugs of abuse cause an increase of dopamine in the nucleus accumbens (NA), a brain region important for immediate rewarding effects. The NA consists of two sub-regions, the NAcore and NAshell. These regions have distinct functions in aspects of addiction. The NAcore is mainly involved in conditioned behaviour as a result of stimuli predicting a motivationally relevant event. In contrast, the NAshell is primarily involved in the rewarding effects of drugs. The prefrontal cortex (PFC) is important for planning and decision making and is connected to the NA via glutamatergic projections. It is hypothesized that alterations in the PFC-NA connection as a result of long-term drug use mediate the persistent nature of addiction, for example by decreased cognitive control. A third brain region, the amygdala, plays an important role in conditioned behaviour by establishing connections between previously neutral stimuli and motivationally rewarding stimuli. The amygdala is therefore strongly involved in cue-induced relapse. Recently, it was discovered that the insula is possibly involved in SUD, in particular in the interoceptive aspects of drug consumption. The insula is connected to the NA, PFC and amygdala.

Different brain regions are potential targets for treatment of addiction with DBS. A majority of the studies have investigated the NA as a putative therapeutic target, making use of several animal models and drugs of abuse. Most studies have shown that NA DBS decreases relapse behaviour, however there seems to be differences between the type of drugs (psychostimulants versus opiates and alcohol) and sub-regions of the NA (NAcore versus NAshell).

Impulsivity

Previous studies have revealed a relationship between addictive behaviour and impulsive behaviour. Many criteria for SUD in the DSM-5, a manual for psychiatry, refer to impaired impulse control. An overview of underlying neurobiological mechanisms of impulsivity is given in chapter 1. There is a large overlap in brain regions that are involved in SUD and impulsivity, such as the NA, PFC and amygdala. Similar to SUD, it is hypothesized that impulsive responding result from an altered PFC-NA connection. This intriguing overlap between SUD and impulsivity provides new opportunities for interventions for SUD aimed at reducing impulsive behaviour.

Several animal models exist to investigate different forms of impulsive behaviour in rodents. These models are extensively described in chapter 1. The animal models are based on human impulsivity tasks, facilitating a translation to the clinical situation. In this thesis, the five-choice serial reaction time task (5-CSRTT), the stop-signal task (SST) and
the delayed reward task (DRT) are used. In the 5-CSRTT, rats learn to respond to a light stimulus in one of five response holes. In case rats respond before a stimulus is presented, it is defined as impulsive behaviour; the inability to inhibit pre-potent actions. Another form of impulsive action is measured in the SST. Rats learn to respond as quickly as possible to a light stimulus. However, in 25% of the trials a stop-signal is presented in the form of a tone, and the planned response must be inhibited. The DRT assess impulsive choice by measuring the preference for immediate small rewards and larger but delayed rewards. A large preference for the immediate rewards is interpreted as impulsive choice. In the animal model, rats choose between a small food reward and a larger food reward which is received after increasing delays.

**Relationship between substance use disorder and impulsivity**

Although a relationship between impulsivity and substance dependence is suggested, it remains unclear what the exact relationship is. For psychostimulants such as cocaine and nicotine it has been shown that different aspects of impulsive behaviour are predictive of addictive behaviour. Increased impulsive behaviour is associated with increased motivation to take drugs and increased chance for relapse. In contrast, the relationship between impulsive behaviour and alcohol and opioid use disorder has received less attention. For this reason, the relationship between heroin self-administration and impulsive choice was investigated in chapter 3. To this end, a group of rats was first trained in the DRT and selected based on individual differences in impulsive choice. Subsequently, they were trained in the heroin self-administration model. In contrast to what was found for psychostimulants, heroin intake, motivation for heroin taking and drug- and cue-induced reinstatement were not dependent on differences in impulsive behaviour. However, impulsive behaviour increased during the period of heroin intake. These results suggest that previous findings of elevated impulsivity levels as observed in heroin-dependent subjects are a consequence of heroin intake.

**Stress and impulsivity**

Many pharmacological interventions that target cue-induced or drug-primed relapse are also effective in models of impulsive behaviour, which stresses the strong relationship between impulsivity and addiction. In addition to drugs and drug related stimuli, acute stress is known to induce relapse. Based on the strong relationship between impulsivity and addiction, it is hypothesized that acute stress may have an influence on impulsive behaviour. In chapter 4, we explored the effects of acute stress on impulsive choice and response inhibition. Acute stress was induced by injection of yohimbine, a competitive α2 adrenoceptor antagonist. Yohimbine mimics the systemic stress response and is
frequently used to study the effects of acute stress. In our hands, yohimbine decreased impulsive choice as measured in the DRT. A baseline-dependent effect was found in the SST; low impulsive animals increased impulsivity as a result of yohimbine and high impulsive animals decreased impulsivity. This study shows that effects of acute stress on impulsive behaviour are dependent on the level of impulsivity. The observed effects are comparable to the effects of cocaine, amphetamine, methylphenidate and nicotine on various types of impulsive behaviour. This similarity can be explained by the effects of both psychostimulants and yohimbine on dopaminergic and noradrenergic neurotransmitter systems. Although we have not explored this further, this is a potential explanation for cross sensitization of stress and psychostimulants; effects of stress on dopaminergic motivation systems that are involved in impulsive behaviour and substance abuse, result in an increased risk of substance abuse and relapse.

Deep brain stimulation for heroin use disorder

In the second part of thesis, the effects of DBS on aspects of substance use disorder and impulsivity are explored. For DBS, two electrodes are implanted in the brain. This offers the opportunity for continuous stimulation, and to reach deep subcortical structures. Stimulation parameters can be adjusted individually and the effects of stimulation are reversible, which are large advantages of this technique. The exact working mechanism of DBS is not yet known. Nowadays it is hypothesized that DBS influences local neurons around the electrode, but also influences passing neurons and thereby a wider neuronal circuitry. Psychiatric disorders, which have been hypothesized to rely on a dysfunctional neuronal network, might therefore benefit from altered neuronal activity by DBS treatment.

The NA seems to be a promising brain target for DBS treatment of SUD, based on its important role in reward and motivation. The effects of DBS of the sub-regions NAcore and NAshell on different aspects of heroin addiction are described in chapter 5. This study was performed in the heroin self-administration model. It can be concluded that NAcore DBS decreases motivation for heroin taking, facilitates extinction behaviour and decreases cue-conditioned reinstatement. NAcore DBS did not alter heroin intake and drug-induced reinstatement. In contrast, NAshell DBS did not alter these aspects. The NAcore sub-region has been shown to be primarily involved in mediating conditioned behaviour in response to cues predicting motivationally-relevant, which possibly explains the specific effects of NAcore DBS as found in this study.
Deep brain stimulation and impulsivity

Impulsivity is a common feature of psychiatric disorders for which the efficacy of NA DBS treatment is currently investigated. Therefore, we aimed to investigate the effects of NACore DBS on impulsive behaviour. Chapter 6 describes the study in which NACore DBS is administered in the DRT and 5-CSRTT, to explore whether the effects of NACore DBS are dependent on the form of impulsive behaviour. The results of both tasks revealed a negative correlation with impulsive behaviour during baseline days (without DBS intervention). This suggests that impulsive rats decreased impulsive behaviour due to NACore DBS treatment and vice versa. These results extend our understanding of the clinical effects of DBS in psychiatric disorders with maladaptive impulsivity, such as SUD and OCD.

Deep brain stimulation for impulsive choice as a consequence of heroin intake

In the final experimental chapter (chapter 7), we aimed to combine the results of chapter 3, 5, and 6. The effect of NACore DBS on impulsive choice as a consequence of heroin intake was explored in a pilot study. Similar to the experimental procedure in chapter 3, rats were first trained in the DRT and consequently in a heroin self-administration paradigm. Throughout heroin self-administration, impulsivity as measured in the DRT was monitored and NACore DBS was applied in the DRT. NACore DBS decreased impulsive choice during the period of heroin taking, but not during extinction. The results of this pilot study suggest that NACore DBS is able to alter heroin induced impulsive choice.

Deep brain stimulation of the insula

A second pilot study is described in the general discussion, chapter 8. Besides the NA, there are other brain regions which are a possible target for DBS intervention for substance use disorder. Recently, the insula was discovered to play a role in addiction, especially in the interoceptive aspects of drug consumption. Most evidence comes from studies based on cigarette smoking. We therefore conducted a pilot study into the effectiveness of insula DBS on reducing nicotine intake and reinstatement. Unfortunately, in our hands, insula DBS did not alter nicotine intake and reinstatement. In contrast, other studies found effects of manipulations of the insula on nicotine intake and reinstatement. Possible explanations for the contradictory results are differences in stimulation parameters and location of DBS electrodes. The insula is a large and heterogeneous brain structure, and the exact location of stimulation can have a large impact on the effects of DBS.
Clinical translation

In conclusion, based on the results from this thesis and other studies, NA DBS is a promising treatment for treatment-resistant heroin use disorder. Important to note is that implementation of DBS for addiction faces additional complicating factors. Drug addicted patients often experience a less stable social environments compared to for example OCD patients, as well as fluctuating and diminished perceived burden of the disease. In addition, the question remains whether DBS is a suitable treatment for poly-drug abuse.

Notwithstanding these critical notes, DBS has been shown to be a powerful research tool that can be used to elucidate underlying pathophysiological mechanisms of complex psychiatric disorders, as well as the therapeutic mechanisms of DBS. Therefore, DBS research is highly relevant to increase our understanding, and to optimize DBS as a therapeutic intervention in treatment-resistant psychiatric patients.